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Original Article

ORIGINAL ARTICLE

A phase IV, randomised, double-blind, controlled, parallel group trial to evaluate the effectiveness and safety of Balneum Plus versus emollient in the treatment of chronic kidney disease–associated pruritus in haemodialysis patients

Jacqueline Nevols [1], Lynn Watkins[2] and Robert Lewis[3]

[1]Consultant Nephrologist, [2]Lead Renal Research Nurse and [3]Consultant Nephrologist, Portsmouth Hospitals University NHS Trust

Correspondence to: Jacqueline Nevols; E-mail: jacqueline.nevols@porthosp.nhs.uk

ABSTRACT

Background. Chronic kidney disease–associated pruritus (CKD-aP) is a common, distressing complaint in patients with advanced renal disease that is frequently overlooked. Treatment is often unsatisfactory. Balneum Plus (Almirall, Barcelona, Spain) is a cream containing 3% lauromacrogols and 5% urea, commonly used to treat atopic dermatitis. It has not been studied in CKD-aP to date.

Methods. Adult haemodialysis patients were randomised 1:1 to apply Balneum Plus or E45 (Reckitt Beckiser, Slough, UK) to compare the active ingredients of lauromacrogol and urea with a control cream. Itch was defined as three episodes of itching during the last 2 weeks, appearing a few times a day, lasting a few minutes and troubling the patient [1]. Patients with other causes of itch, e.g. eczema and liver disease, were excluded. The primary outcome was a reduction in itch as measured by the visual analogue scale (VAS) score at 4 weeks and analysed using an analysis of covariance approach.

Results. A total of 314 patients were screened and 58 patients were randomised, 29 in each group. Three patients dropped out in each group. The median baseline VAS scores were 6.5 [interquartile range (IQR) 4.4–8.0] in the Balneum Plus group and 6.3 (IQR 5.1–7.3) in the E45 group. After 4 weeks, VAS scores decreased to 2.6 (IQR 0.9–4.5) and 2.0 (IQR 0.5–4.8) in the Balneum Plus and E45 groups respectively ($P = 0.64$ for the difference). Using a validated questionnaire to assess secondary outcomes, we found that the Balneum Plus group had longer itching episodes, more difficulty staying asleep and itching was more annoying than in the E45 group. There was no significant difference in adverse events between the two groups. One patient reported inflamed spots on the abdominal skin in the Balneum Plus group.

Conclusion. This is the first randomised controlled study of two different emollients for the treatment of CKD-aP and is a negative study. We found no significant difference in itch scores between Balneum Plus and E45.

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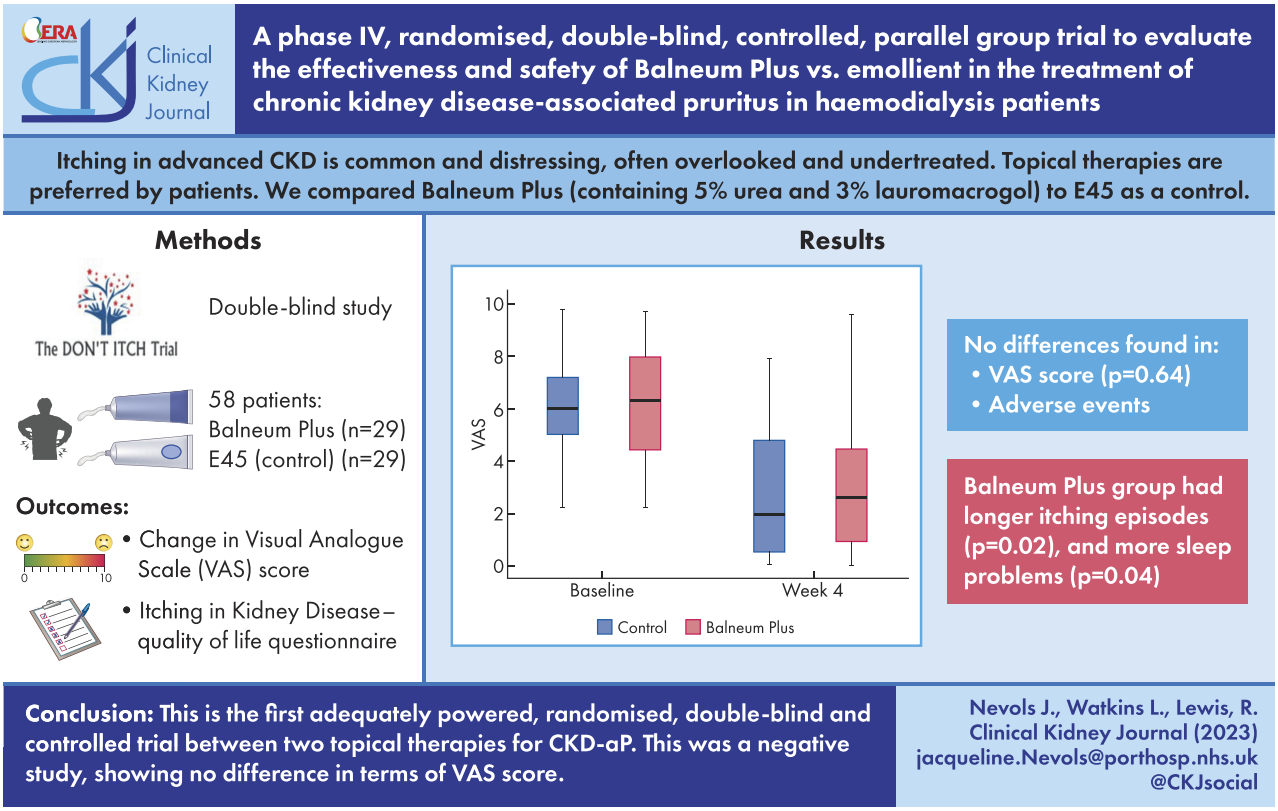
LAY SUMMARY

Itching is a common complaint among patients with advanced kidney disease that reduces quality of life and is associated with decreased patient survival. Treatment options are limited and often have side effects. Topical treatments are preferred by patients but have not been widely studied to date in controlled trials. We performed a randomized controlled trial of two commercially available skin creams, Balneum Plus (which contains a local anaesthetic) and E45 cream as a control, in patients undergoing haemodialysis. Patients scored the intensity of their itching before and after 4 weeks of applying the cream twice daily. We found that there was no difference in the effectiveness between the creams. There were no serious side effects during the study. Following the study, we make every effort to encourage the regular use of an emollient in renal patients who suffer from itching.

GRAPHICAL ABSTRACT



Keywords: clinical trial, haemodialysis, pruritus, quality of life, therapy

INTRODUCTION

Chronic kidney disease–associated pruritus (CKD-aP), or uraemic pruritus, is a common and troubling complaint among patients with renal disease [2, 3]. A large, recent study found that 37% of dialysis patients are at least moderately bothered by itching [4]. CKD-aP is underestimated as a symptom and underreported by patients [5]. However, recent advances in the understanding of the pathophysiology has led to renewed interest and confidence in the management of this distressing condition. CKD-aP is associated with increasing age, inflammation and hepatitis B and C [5]. There are four main theories for the underlying pathophysiological mechanism, including toxin deposition, peripheral neuropathy, immune system dysregulation and imbalance within the opioid system [2, 6, 7]. CKD-aP reduces health-related quality of life and is associated with reduced survival, probably mediated by sleep disruption [8, 9].

The only well-studied treatment with high-quality evidence of its effectiveness, and recommended by a recent Cochrane review [10], is gabapentin. Its use can be limited by side effects of dizziness and somnolence. Difelikefalin is a kappa-opioid agonist that has been shown to provide clinically meaningful benefits in itching [11]. Its use is limited by being an intravenous drug and side effects of vomiting, diarrhoea and dizziness in some. Evidence for other treatments is weak and there has been an

urgent call for randomised controlled trials [12], with CKD-aP being identified as a key research priority by patients [13].

Topical treatments are preferred by patients [5] and are recommended as first-line therapies for CKD-aP [14]. In CKD, skin dryness (xerosis) due to atrophy of secretory glands and a thickened basement zone results in reduced hydration of the stratum corneum [15]. Xerosis is present in 85% [16] of dialysis patients and may contribute to the intensity of itching [17]. Emollients are designed to improve skin barrier function and prevent transepidermal water loss and the entry of irritants. They are first-line treatments in other pruritic skin conditions such as atopic dermatitis [18], but there are no RCTs of emollients in CKD-aP. An emollient with high-water content was given twice daily to haemodialysis (HD) patients in a non-randomised, non-blinded study of 20 patients and was shown to improve itch scores [19]. Another non-controlled and non-randomised study of aqueous cream showed improvement in itch reported in 16 of 21 patients [20]. In a randomised double-blind study of glycerin and paraffin in 99 uraemic xerosis patients, an improvement was seen in 73%, compared with 44% of those using the control [21], although the study included design flaws with patients acting as their own controls.

Many topical therapies have been investigated, but none so far have shown a proven benefit [2]. Lauromacrogols (polidocanols) are topical local anaesthetics that are widely used in atopic dermatitis [22]. They have been shown to reduce cowhage-induced itching (a histamine-independent pathway) in healthy volunteers [23] and show improvements in xerotic eczema [24] and dry dermatoses [25]. In a post-marketing survey (observational cohort study) of 3566 patients [26], the majority of whom had atopic dermatitis, a bath oil containing lauromacrogol reduced itching. Moderate to severe pruritus was seen in 75% of patients before treatment and 87% had no or only slight pruritus afterwards. Only 0.28% had mild skin reactions to the treatment. Importantly, 60% of patients were able to reduce the use of other therapies, providing a cost saving. Although not a blinded or controlled study, this study provides a reflection of daily practice. In another post-marketing survey of a polidocanol–urea preparation in 1611 patients with a variety of skin conditions [27], half the patients reported they were free of itching by the end of the observation period. Side effects were noted in only 2.8% of patients. Lauromacrogols have been reported as successful therapy in other case reports [28, 29]. Thus lauromacrogol appears to be a promising and safe treatment for pruritus and there have been calls for this substance to be investigated in a clinical setting [18]. The Don't Itch trial is a monocentric study designed to test the efficacy of this substance in CKD-aP.

MATERIALS AND METHODS

The study received ethical approval from the local ethics committee (reference 15/SC/0478) and was registered with EudraCT (2014-005594-36) and ISRCTN (ISRCTN13971661) as a clinical trial of an investigational medicinal product. Study participants were approached by nursing staff of the dialysis unit and asked if they were troubled by itching and willing to participate in a clinical trial. If so, they were given a patient information sheet and a minimum of 48 hours to consider their participation before the informed consent process. Balneum Plus (Almirall, Barcelona, Spain) is a white, smooth cream containing 3.0% lauromacrogols and 5.0% urea. The emollient control cream was E45 cream (Reckitt Beckiser, Slough, UK), which is used as part of standard care in patients with CKD-aP. This cream looks identical to Balneum Plus but does not contain the active ingredients of lauromacrogols or urea. The emollient control may be expected to have some beneficial effect on the dry skin that patients with end-stage renal disease (ESRD) experience (uraemic xerosis). We were testing the effect of the active ingredients (lauromacrogols and urea) on the intensity of itching caused by CKD-aP. Other trials have used simple emollient as their control cream [30, 31]. If, prior to the trial, patients were using a simple emollient to treat their itching, they were asked to substitute this for the trial cream.

Inclusion criteria

The participants had to meet all the following criteria to be considered eligible for the study:

- Age ≥18 years.
- Receiving HD for at least 3 months.
- Willing and able to give informed consent.
- Self-reported symptoms of CKD-aP (itch was defined as above) [1].
- VAS score of at least 2 cm.

Exclusion criteria

Individuals were excluded for the following reasons:

- Other skin condition reported by the patient or noted in the medical records (e.g. psoriasis, atopic dermatitis) unless the area of skin affected by CKD-aP is on a separate part of the body.
- Taking oral medication for CKD-aP other than antihistamines (e.g. opiates or gabapentin) unless prescribed for another indication (e.g. chronic pain) and itching still persists (and not thought to be a side effect of the drug).
- Acute erythroderma, acute inflammatory, oozing or infected skin lesions.
- Use of topical medication containing any active ingredients (anything other than simple emollient).
- Any severe, chronic liver disease.
- Active, known solid organ malignancy.
- Cognitive impairment that may impact on their ability to complete the questionnaire (e.g. severe dementia).
- Lack of a good understanding of English.
- Unwilling to apply the topical treatment as prescribed, including a previous history of poor compliance with any treatment.
- Significant ongoing illness requiring inpatient treatment.
- Allergy to Balneum Plus or any of its ingredients.
- Breastfeeding.

Eligible participants were stratified for antihistamine use and then randomised 1:1 using permuted blocks to receive either Balneum Plus or E45 as emollient control. The randomisation lists were generated using Stata (StataCorp, College Station, TX, USA) and sent to the clinical trials pharmacist and kept securely in the hospital pharmacy. Upon receipt of notification of participant entry, a treatment pack was prepared, labelled with the participant's unique trial number and dispensed according to the treatment allocation. All treatment packs looked identical. The investigators, research nurses and participants were all blinded

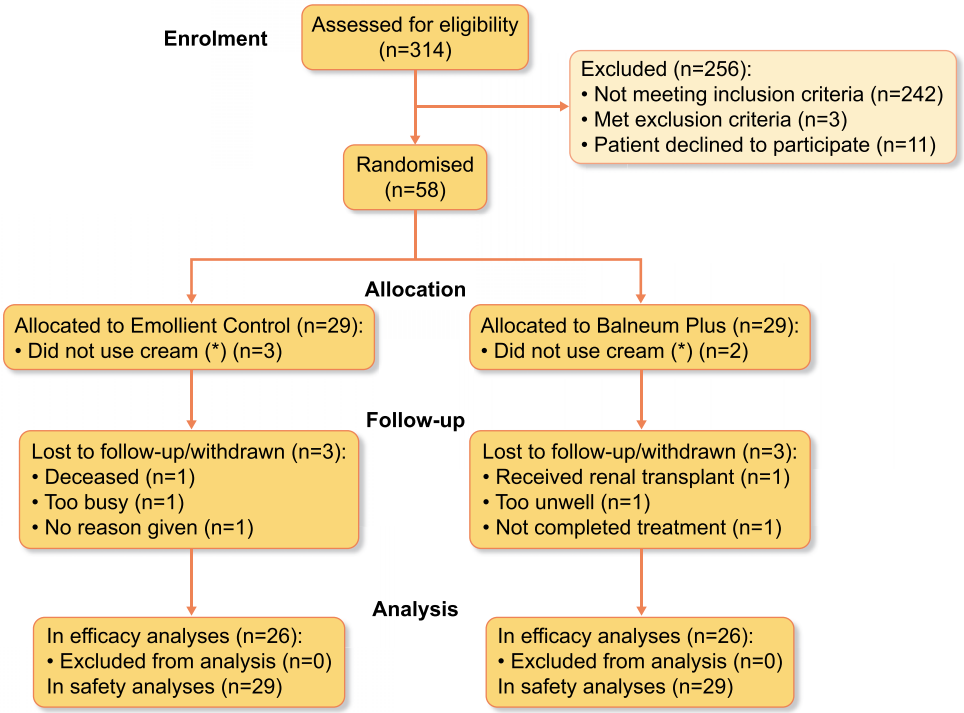


Figure 1: CONSORT diagram for the Don't Itch trial.

to the treatment allocation. See the flow diagram in the supplementary material.

Baseline visit

Participants were asked to mark the intensity of their itch on a VAS—a 10-cm line printed on paper with 'No itch' at one end and 'Worst imaginable itch' at the other. They were then asked to complete the Itching in Kidney Disease questionnaire [1]. The majority of questions were yes/no or tick box style.

Participants were told to apply the study cream liberally, twice daily, to all affected areas, avoiding mucous membranes, as though applying sunscreen. The following were assessed by a research nurse at weekly follow-up visits:

- Visits 1–3: Participants completed a VAS to score their itching intensity. They were asked how often they apply the cream to check compliance. Any changes to the participant's medications were recorded. Any adverse events were recorded.
- Visit 4: Patients completed a VAS and recorded adverse events and compliance as above. They were also asked to complete the quality-of-life questionnaire again. Patients were seen 1 week after finishing the trial to collect data on adverse events. The study visits were undertaken during routine HD sessions.

STATISTICAL ANALYSIS

We recruited 58 patients for the study based on the following sample size calculation. A reduction in VAS score by 2 cm is considered representative of a significant treatment effect. This value has been used in other trials of treatments for CKD-aP [32–34]. Therefore, we only recruited patients with a VAS score ≥2 cm. We factored in a correlation between the starting VAS score and the follow-up score, using an analysis of covariance (ANCOVA) approach. This takes into account the fact that patients with the highest initial VAS score will have the most benefit and that those with a lower score have less room for improvement. We set the correlation relatively low at 0.3. Using this approach should minimise the potential selection bias of recruiting only those with the most to gain from the treatment. In our study, we aimed for 90% power and took the significance level at 5%. Based on a standard deviation (SD) of 2.3 (taken from a service evaluation of the VAS), assuming a correlation between pre- and post-measurements of 0.3, a 5% significance level and 90% power, we needed 26 patients per group, giving 52 patients in total. We assumed that there would be an approximate 10% dropout rate, thus we arrived at a total sample size of 58 required for the study. We stratified the patients according to oral antihistamine use to ensure equal numbers of these patients in each group.

The primary endpoint was itch intensity as measured by the VAS after 4 weeks of treatment. This outcome was compared between groups using ANCOVA. The itch intensity at the end of the study was considered as the outcome variable, with the itch intensity at pretreatment (baseline) and the use of antihistamines (a stratification factor in the randomisation) as covariates in the analysis. The VAS scores were found to have a positively skewed distribution. To meet the assumptions of the analysis methods, a log transformation was made, with the analysis performed on a log scale. Due to the log transformation, the relative covariate-adjusted difference (ratio) in VAS scores between groups was reported, with a corresponding 95% confidence interval (CI). For the primary analyses, only observed data were analysed. Missing data were assumed to be missing at random. For the sensitivity analysis of the primary outcome, missing data values at 4 weeks were imputed using a last observation carried forward (LOCF)

Table 1: Patient demographics and baseline variables.

Variable	Category	Control ($n = 29$)	Balneum Plus ($n = 29$)
Age (years), mean ± SD		63.4 ± 16.2	64.0 ± 13.9
Gender, *n* (%)	Female	9 (31)	9 (31)
	Male	20 (69)	20 (69)
Smoking status, *n* (%)	Never smoked	11 (38)	11 (38)
	Ex-smoker	12 (41)	13 (45)
	Current smoker	6 (21)	5 (17)
Time on HD (years), median (IQR)		2.6 (0.9–4.7)	1.5 (0.7–3.4)
Cause of ESRD[a], *n* (%)	Glomerulonephritides	3 (12)	9 (33)
	Diabetic neuropathy	8 (32)	3 (11)
	Hypertension/RVD	4 (16)	8 (30)
	Obstructive uropathy	5 (20)	2 (7)
	Kidney disease	2 (8)	1 (4)
	Other	3 (12)	4 (15)
Type of dialyser	Small	7 (24)	6 (21)
	Medium	12 (41)	11 (38)
	Large	10 (34)	12 (41)

RVD: renovascular disease.
[a]Unknown cause for six patients: four control and two Balneum Plus.

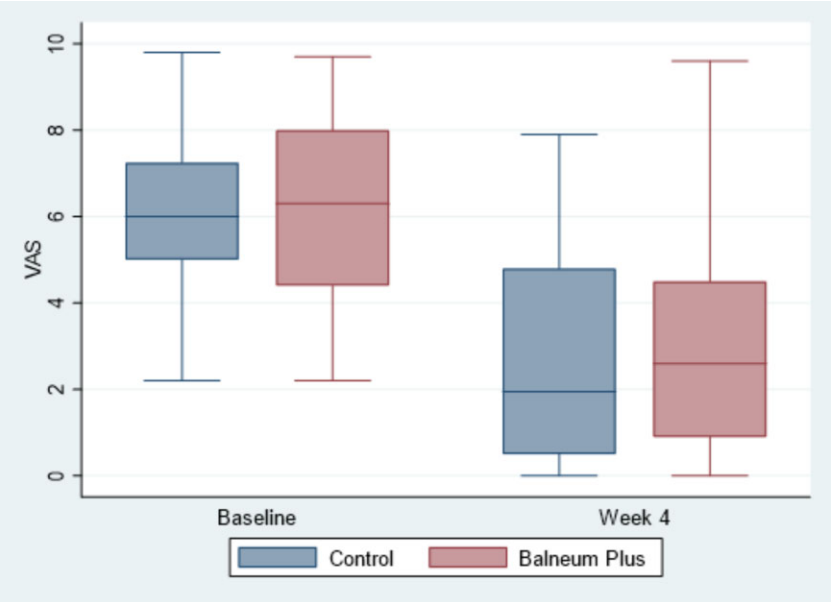


Figure 2: Box and whisker plot illustrating the VAS scores at baseline and after 4 weeks of twice daily application of Balneum Plus and E45 control.

approach. Only post-baseline VAS scores (from week 1 onwards) were carried forward, with no imputation made for patients with VAS scores at baseline only.

The first secondary outcome was the amount of cream used. The responses were not found to follow a normal distribution, thus the Man—Whitney test was used to compare between groups. Further secondary outcomes were data from the kidney questionnaire at 4 weeks. Each item from the questionnaire was considered as a separate outcome, with no overall score generated. All questionnaire items were categorical in nature, with a mixture of binary and ordinal questions. Binary items were compared between the two study groups using Fisher's exact test. Additionally, ordinal items were analysed using the Mann–Whitney test to allow for the natural ordering of the response categories. The final analyses compared the occurrence and number of adverse events (AEs) and serious adverse events (SAEs) per patient between groups. Fisher's exact test was used to compare the occurrence of AEs and SAEs between groups, while the Mann–Whitney test was used to compare the number of such events.

A trial steering committee met at intervals during the study to provide supervision of the trial. Data collection and adherence to the study protocol were monitored frequently by the sponsor. The protocol was peer reviewed by two independent consultant nephrologists. One HD patient was involved in the design of the patient report forms and questionnaire to improve 'user friendliness'. The Wessex Kidney Patient Association was supportive of the study. The study was carried out in accordance with the Declaration of Helsinki.

RESULTS

A total of 314 patients were assessed for eligibility: 242 did not meet the inclusion criteria, 3 patients met exclusion criteria

Table 2: Kidney questionnaire results at 4 weeks.

		Control		Balneum Plus		
Question	Category	*N*	*n* (%)	*N*	*n* (%)	*P*-value
Frequency of itching	Daily	25	20 (93)	25	20 (80)	1.00
	Weekly		4 (16)		4 (16)	
	Fortnightly		0 (0)		0 (0)	
	≤Monthly		1 (4)		1 (4)	
Length of itching episode	<30 min	25	14 (5)	25	6 (24)	**.02**
	30 min–1 hour		4 (16)		5 (20)	
	1–4 hours		3 (12)		5 (20)	
	4–24 hours		2 (8)		3 (10)	
	Constant		2 (8)		6 (24)	
Difficulty falling asleep	Never	26	10 (38)	25	9 (36)	1.00
	Sometimes		9 (35)		10 (40)	
	Always		7 (27)		6 (24)	
Difficulty staying asleep	Never	26	20 (77)	25	12 (48)	**.04**
	Sometimes		3 (12)		7 (28)	
	Always		3 (12)		6 (24)	
Need sleeping tablets	Never	26	19 (73)	25	23 (92)	.08
	Sometimes		3 (12)		1 (4)	
	Always		4 (15)		1 (4)	
Effect of dialysis on itching	Improves itching	26	0 (7)	25	0 (0)	.24
	No effect		20 (77)		15 (60)	
	Makes itching worse		6 (23)		10 (40)	
Does itching affect quality of life	No	26	16 (62)	25	9 (36)	.10
	Yes		10 (38)		16 (64)	
Effect of itching on anxiety	No difference	26	22 (79)	25	15 (68)	.202
	Makes it worse		4 (15)		8 (32)	
Effect of itching on low mood	No difference	26	20 (77)	25	16 (64)	.37
	Makes it worse		6 (23)		9 (36)	
Effect of itching on ability concentrate	No difference	26	20 (77)	25	14 (56)	.14
	Makes it worse		6 (23)		11 (44)	
Effect of itching on appetite	No difference	26	25 (96)	25	22 (88)	.35
	Makes it worse		1 (4)		3 (12)	
Effect of itching on sexual desire	No difference	26	26 (100)	25	22 (88)	.11
	Makes it worse		0 (0)		3 (12)	
Effect of itching on sexual function	No difference	26	25 (96)	25	23 (92)	.61
	Makes it worse		1 (4)		2 (8)	
Itching is bothersome	Not at all	26	8 (31)	25	6 (24)	.47
	Mildly		6 (23)		5 (20)	
	Moderately		9 (35)		10 (40)	
	Severely		3 (12)		4 (16)	
Itching is annoying	Not at all	26	11 (42)	25	1 (4)	**.006**
	Mildly		5 (19)		3 (12)	
	Moderately		5 (19)		15 (60)	
	Severely		5 (19)		6 (24)	
Itching is unbearable	Not at all	26	16 (62)	25	12 (48)	.24
	Mildly		4 (15)		2 (8)	
	Moderately		2 (8)		5 (20)	
	Severely		4 (15)		6 (24)	
Itching is worrying	Not at all	26	22 (79)	25	20 (76)	.37
	Mildly		2 (8)		2 (8)	
	Moderately		2 (8)		1 (4)	
	Severely		0 (0)		3 (12)	

Analysis using Mann–Whitney test or Fisher's exact test.

and 11 declined to take part. A total of 58 patients were randomised, 29 in each group. Three patients were lost to follow-up in the Balneum Plus group (one received a transplant, one was too unwell and another did not complete the treatment) and three were lost to follow-up in the E45 group (one patient died, one was too busy and one due to uncertain reasons) (Fig. 1).

The two groups were evenly matched in terms of age, gender, smoking status and dialysis parameters (see Table 1). Baseline kidney questionnaire answers were similar in both groups, with

Table 3: Adverse events.

Outcome	Category	Control ($n = 29$)	Balneum Plus ($n = 29$)	P-value
Patient had AE, *n* (%)	No	24 (83)	23 (79)	1.00
	Yes	5 (17)	6 (21)	
AEs per patient, mean ± SD		0.17 ± 0.38	0.31 ± 0.71	.66
Patient had SAE, *n* (%)	No	26 (83)	25 (86)	1.00
	Yes	3 (10)	4 (14)	
SAEs per patient, mean ± SD		0.10 ± 0.31	0.21 ± 0.56	.63

86% of subjects in the Balneum Plus group and 93% of subjects in the control group experiencing itching on a daily basis.

Primary efficacy analysis

The results for the primary outcome are shown in Fig. 2. The baseline VAS score of 6.5 [interquartile range (IQR) 4.4–8.0] decreased to 2.6 (IQR 0.9–4.5) in the Balneum Plus group after 4 weeks. Similarly, in the E45 group, the VAS score decreased from 6.3 (IQR 5.1–7.3) to 2.0 (IQR 0.5–4.8) ($P = 0.64$ for the difference). The differences between the groups were adjusted for the baseline VAS score and also the use of antihistamines. Thus no significant difference in the VAS itching scores was observed between the two groups. The findings were similar when only the observed scores were analysed, and also for the sensitivity analysis where missing values were imputed.

Secondary outcomes analysis

Patients in the Balneum Plus group used a median of 218 g of cream (IQR 82–300) and those in the E45 group used a median of 137 g (IQR 61–317) ($P = 0.75$ for the difference). This suggests that there was no significant difference in the cream used between the Balneum Plus and control groups. The kidney questionnaire results suggested that the majority of measures examined did not significantly vary between the two groups. Significant differences were observed for some measures (see Table 2). These appeared to indicate a worse outcome in the Balneum Plus group than in the control group. The length of itching episodes at 4 weeks was longer in the Balneum Plus group. More than a third (34%) of this group had itching that lasted >4 hours, compared with only 16% of the control group. The Balneum Plus group also had more difficulty staying asleep, as 52% of patients had some difficulty staying asleep compared with only 24% of the control group. Patients in the Balneum Plus group also found itching to be more annoying, as 84% of the Balneum Plus group indicated that itching was moderately or severely annoying compared with only 38% of the control group.

Adverse events

There was no significant difference between groups in terms of the proportion of patients who experienced an adverse event. Six patients (21%) in the Balneum Plus group had an AE compared with 5 (17%) in the control group (see Table 3). SAEs occurred in 4 (14%) in the Balneum Plus group and 3 (10%) patients in the control group, the majority involving problems with dialysis access. The majority of AEs were unrelated to the study. Only one AE was found to be possibly related to the study, with one patient in the Balneum Plus group developing inflamed spots on their abdominal skin.

DISCUSSION

The Don't Itch trial was designed to test the efficacy of Balneum Plus in CKD-aP. We found no significant difference between Balneum Plus and E45 in terms of the VAS score after 4 weeks of treatment. Some of the secondary outcome measures suggest a slightly worse outcome for patients using Balneum Plus, with itching being described as more annoying, longer lasting and interfering with sleep more so than for patients using the control. Both creams were well tolerated, with no serious side effects noted during the study. Following completion of this study, we make every effort to ask patients about their symptoms during dialysis appointments. We have developed an information leaflet to help patients manage their pruritus, including basic skin care advice. We offer tester pots of creams for patients to try at home to see which cream suits their specific symptoms. The main limitation of this study is that we did not include a group of patients using no treatment. We did not feel it was ethical to ask a patient with itching not to apply any cream to their skin for a period of 4 weeks. Thus, due to the design of the study, we have not shown that emollients improve itching in CKD-aP per se, only that there is no difference between Balneum Plus and E45 treatment. Although this was a negative study, we believe that taking symptoms seriously and encouraging the regular use of an emollient can reduce the significant burden of itching in these polysymptomatic patients.

SUPPLEMENTARY DATA

Supplementary data is available at *ckj* online.

ACKNOWLEDGEMENTS

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The study was funded by Almirall (UK).

AUTHORS' CONTRIBUTIONS

J.N. designed the study, sought appropriate approvals and acted as chief investigator. L.W. was the lead renal research nurse. R.L. was the lead for renal research.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study will be available upon request from the lead author.

CONFLICT OF INTEREST STATEMENTS

None declared.

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