

ORIGINAL ARTICLE

The regular use of an emollient improves symptoms of atopic dermatitis in children: a randomized controlled study

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Abstract

Background Emollients are considered as a first-line therapy for the treatment of atopic dermatitis (AD). However, evidence-based proof that the regular use of emollients reduces AD severity is lacking.

Objective To assess whether the regular use of emollients results in a reduction in AD severity in children with AD.

Methods In this multicentre randomized, parallel group, open-label study, children with mild-to-moderate AD were recruited during a flare. After flare resolution with a topical corticosteroid, patients were randomized to V0034CR emollient, reference emollient or no emollient (1:1:1 ratio), for 12 weeks. AD severity was assessed regularly by physicians [Scoring for Atopic Dermatitis (SCORAD) and subcomponents, IGA] and by parents (PO-SCORAD and POEM).

Results A total of 335 patients were randomized to V0034CR ($n = 111$), reference emollient ($n = 116$) or no emollient ($n = 108$). After 12 weeks of treatment, SCORAD score was reduced by 5.28 points in the V0034CR group and by 3.36 points in the reference emollient group compared with the no emollient group (+4 points; $P < 0.001$ in both emollient groups vs. no emollient group). In a similar manner, PO-SCORAD score was reduced by 4.88 and 2.67 points in the V0034CR and reference emollient groups, respectively, but increased by 2.90 points in the no emollient group ($P < 0.001$). Similar results were observed for POEM. A continuous decrease in all scores was observed over the 12-week treatment period. At the end of the study, the percentage of patients in complete remission (i.e. without a new flare over the treatment period) was higher in the V0034CR (59.5%) and reference emollient (44.3%) groups than in the no emollient group (29.8%; $P < 0.001$).

Conclusion These results demonstrate that the regular use of emollients in children with mild-to-moderate AD reduces the severity of symptoms and, therefore, support their use as a first-line treatment for these patients.

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Conflicts of interest

GST, FB, PK, LM and AK received investigator fees from Pierre Fabre. CL, MSA and AD are employed by Pierre Fabre.

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease, usually appearing within the first 5 years of life and affecting up to 15% of children in industrialized countries.^{1–4} The disease evolves through the alternation of flares followed by phases of remission.⁵ Major symptoms of AD are xerosis (i.e. cutaneous

dryness), intense pruritus and eczematous lesions related to impaired skin barrier function.^{6–10}

Atopic dermatitis flares are usually treated with topical corticosteroids to reduce inflammation and pruritus. Skin hydration by emollient therapy reduces xerosis and, therefore, pruritus and improves the skin barrier function.¹¹ Importantly, all consensus

conferences and guidelines support the use of emollients as a first-line therapy for the treatment of AD.^{12–14}

This study aimed to evaluate the benefit of regular use of emollients in the management of mild-to-moderate AD. Data regarding primary efficacy endpoints have already been published elsewhere.¹⁵ Both emollients have proven to be more efficient in reducing the percentage of patients with at least one flare during the study compared to children without emollient treatment (35.1% of patients experienced at least one flare in the emollient-treated group vs. 67.6% in the no emollient group).¹⁵ In addition, fewer patients treated with emollient required corticosteroids/immunosuppressants compared to patients without emollient treatment (23.6% vs. 43.3%, respectively).¹⁵ Herein, we specifically assessed whether the regular use of emollients results in a reduction in severity of AD symptoms.

Materials and methods

This was an international, multicentre, randomized, parallel group, open-label study in children aged 2–6 years with mild-to-moderate AD, diagnosed according to the UK Working Party criteria.¹⁶ The study (EudraCT number: 2012-004621-24) was performed at 27 centres across five countries (France, Estonia, Lithuania, Poland and Romania) in accordance with Good Clinical Practice and was approved by the corresponding Ethics Committees. Parents provided written informed consent for their child's participation.

Study design

Patients were included during a flare (Fig. 1), treated with a potent topical corticosteroid (0.1% desonide; Locatop®; Pierre Fabre Dermatologie, Toulouse, France) applied twice daily until complete resolution of inflammatory signs, for a maximum of 21 days. Lesions were considered resolved if the following criteria were fulfilled: objective Scoring for Atopic Dermatitis (SCORAD) score <15, no lichenification, excoriation, oozing, crusts, oedema, papulation, pruritus or sleep disorders (<1 on the SCORAD visual analogue scale), erythema intensity absent or mild (with residual erythema area ≤10% of extent). Xerosis was to remain present with an intensity of at least mild.

The investigator allocated treatment numbers (given centrally through an interactive voice response system, IVRS) in accordance with the sponsor-generated randomization list, assigning patients to one of three groups (1:1:1) for 12 weeks of treatment with either V0034CR emollient, reference emollient (active control) or no emollient.

Treatments were made with products from a same class with documented proofs of efficacy in atopic dermatitis.^{15,17–19} They were applied according to the product monographs. V0034CR (Dexeryl®; Pierre Fabre Médicament, Toulouse, France), containing glycerol 15%, liquid and soft paraffin 10%, was applied twice daily (8 g per application) to the whole body (and face). The reference emollient (Atopiclair®, Sinclair Pharma, London, United Kingdom) was applied three times daily to areas of the skin affected, or usually/previously affected, by AD.

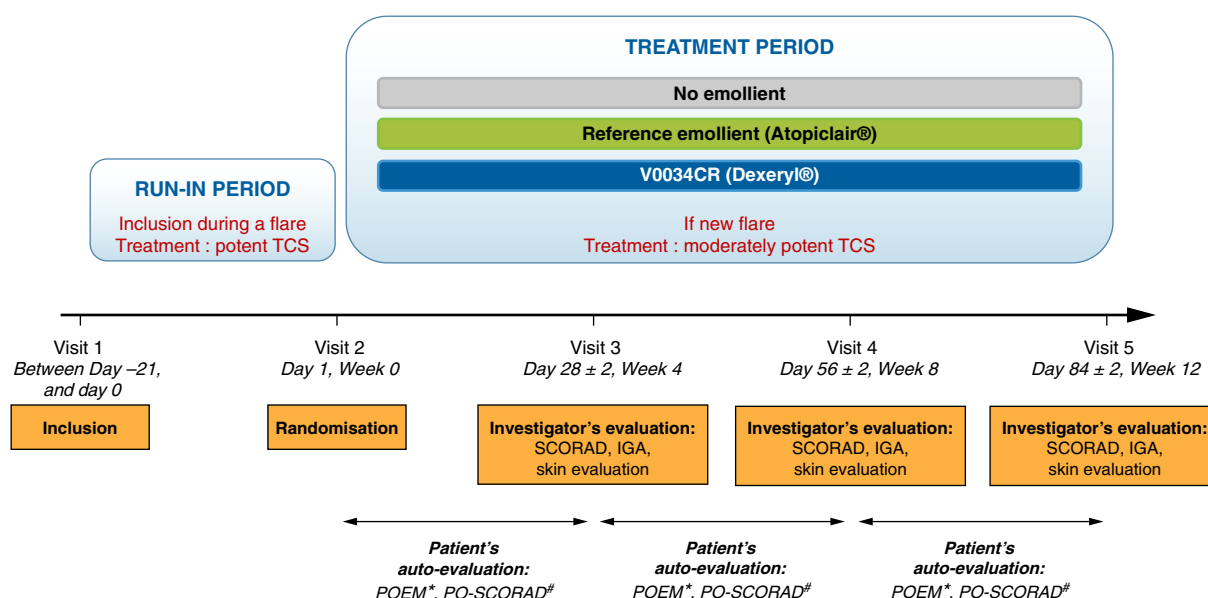


Figure 1 Study design.

During treatment, flares confirmed by the investigator were treated with a moderately potent topical corticosteroid (0.1% desonide; Locapred®; Pierre Fabre Dermatologie) once daily, until complete resolution.

Patient population

Eligible patients had at least one duly documented flare treated with corticosteroids within 6 months of inclusion and a current mild-to-moderate flare with an objective SCORAD (range 0–83) of between 15 and 40 (grade 3).²⁰ Children were excluded if they had other chronic eczemas; bacterial, viral, fungal or parasitic skin infection; ulcerated lesions, acne or rosacea; other dermatological diseases which could interfere with assessment; immunosuppression; history of serious disease; oral corticosteroid or immunosuppressant use (within 14 days); topical corticosteroid, systemic or local antibiotic, non-steroid anti-inflammatory drug or antihistamine use (within 7 days).

Assessments

The different SCORAD scores and subcomponents (objective SCORAD, xerosis, pruritus and sleep loss scores),^{20,21} were calculated by the investigator at each visit (i.e. at weeks 4, 8 and 12). The Patient-Oriented SCORAD (PO-SCORAD),^{22,23} dryness score and Patient-Oriented Eczema Measure (POEM) score²⁴ were evaluated by parents/guardians on a weekly (POEM) or twice weekly (PO-SCORAD and dryness score) basis over the 12-week treatment period.

The number of patients with complete remission (≥ 8 weeks without a flare or anti-inflammatory drugs) was also evaluated at weeks 8 and 12. A flare was defined by at least one of the following conditions assessed by the investigator: measurable increase in lesions (extent/intensity) occurring within <2 weeks; significant increase ($>25\%$) in AD severity evaluated by the SCORAD or PO-SCORAD; and clinical need for topical corticosteroid treatment. Furthermore, patients who withdrew prematurely for inefficacy of treatment, worsening, unknown/missing reason or loss of follow-up were considered as having a flare (i.e. failures). Two separate flares were recorded if topical corticosteroid use was interrupted for ≥ 7 days.

Statistical analysis

Efficacy criteria were described for the full analysis set using SAS® software (version 9.3, Cary, NC, USA).

The percentage of patients with complete remission was compared between active groups vs. the no emollient group using a CMH test stratified by centre (pooled according to the type of structure, the specialty of the investigator and the country).

For xerosis, pruritus and sleep loss scores, SCORAD and objective SCORAD, a mixed model for repeated measures (MMRM) was performed on observed-case data from baseline to Day 28 (week 4), Day 56 (week 8) and Day 84 (week 12) to evaluate the global evolution of the different scores. The model

included treatment group, centre and week as fixed factors, treatment group-by-week interaction and baseline score as covariates, and patient as a random factor. PO-SCORAD, dryness and POEM scores were analysed using an MMRM on observed-case data, from baseline to each theoretical week (calculated accordingly to the day of evaluation).

Results

Patients

Patients were included between February and March 2013, then September and November 2013. A total of 347 children were included, 335 of whom were randomized; 316 completed the study and 19 were withdrawn, most frequently for ‘efficacy concern’ ($n = 9$; Fig. 2). The 335 patients were randomized to V0034CR ($n = 111$), reference emollient ($n = 116$) or no emollient ($n = 108$).

More females were allocated to V0034CR (62.2%) and more males to reference emollient (56.0%; Table 1). Mean age was 4.08 years, mean time since diagnosis of AD was 34 months, 71.3% of patients had a family history of atopy, and other atopic syndromes (asthma and rhinitis) were present in 23.9% of patients (Table 1).

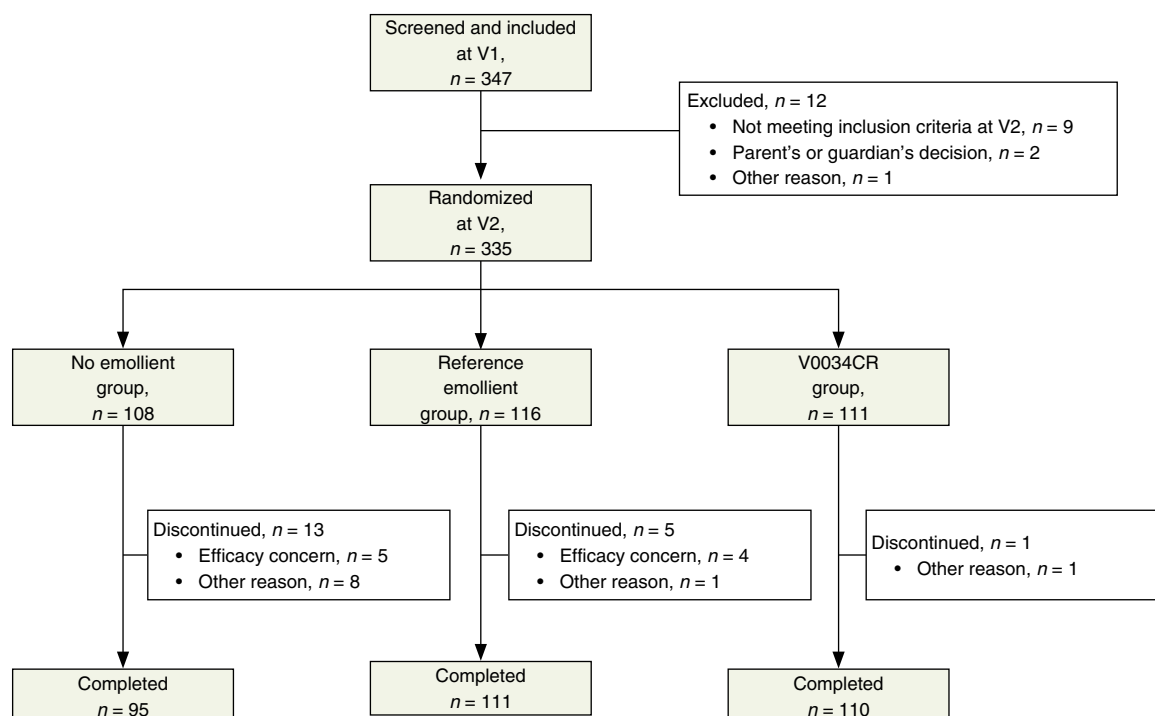
At inclusion, objective SCORAD was between 15.2 and 39.9, and flare severity was rated moderate (74%) or mild (23.6%) by the investigator. At randomization, objective SCORAD was between 3.5 and 14.74, and all flares were rated clear or almost clear by the investigator.

Evolution of AD symptoms during the treatment period

Investigator’s assessments SCORAD scores, calculated by the investigator at each planned visit (i.e. at weeks 4, 8 and 12), were reduced during the 12-week treatment period only in the V0034CR and reference emollient groups, but not in the no emollient group (Table 2). This improvement was statistically significant after 4 weeks of treatment for V0034CR and after 8 weeks of treatment for the reference emollient ($P < 0.0001$). After 12 weeks, baseline SCORAD and objective SCORAD scores were reduced by 5.28 points and 5.48 points, respectively, for the V0034CR group, and by 3.36 points and 3.80 points, respectively, for the reference emollient group.

Xerosis score remained stable during the 12-week treatment period in the no emollient group, but was reduced markedly after 4 weeks of treatment in the V0034CR and reference emollient groups (Fig. 3a). Further improvements in the xerosis score were observed after 8 and 12 weeks of treatment in the V0034CR and reference emollient groups.

Pruritus and sleep loss scores were both increased over the 12-week treatment period in the no emollient group (1-point increase between baseline and week 12 for pruritus score and 0.45-point increase for sleep loss score; Table 3). This increase



	No emollient n = 108	Reference emollient n = 116	V0034CR n = 111	Total n = 335
Full analysis set	108	116	111	335
Per protocol population	97	99	98	294

Figure 2 Patient flow chart.

was significantly lower in the V0034CR and reference emollient groups compared with the no emollient group after 12 weeks of treatment (respectively, 0.10-point, $P < 0.0001$ and 0.29-point, $P < 0.001$ for pruritus score; 0.05-point, $P = 0.005$ and 0.13-point, $P = 0.022$ for sleep loss score).

The compliance to the treatment and to the study was good as the extent of exposure was 79.8 (standard deviation SD = 19.8), 82.8 (SD = 11.1) and 84.5 (SD = 6.1) days for the no emollient, Atopiclair and V0034CR groups, respectively. The average daily quantity used during the study treatment (i.e. from first to last study product application) was 10.7 (± 3.9) g/day for V0034CR.

Parent's assessments PO-SCORAD score increased during the 12-week treatment period (compared to the baseline value calculated at randomization) in the no emollient group (Table 4). In contrast, PO-SCORAD score decreased over the

treatment period in both the V0034CR and reference emollient groups ($P < 0.0001$ vs. no emollient group; Fig. 3b). This reduction was already visible after 1 week of treatment with V0034CR (−1.24 point compared to baseline) and after 6 weeks of treatment with reference emollient (−0.64 point compared to baseline). At the end of the treatment period, PO-SCORAD score was reduced significantly in the V0034CR and reference emollient groups compared to the no emollient group (−7.77 and −5.56 points, respectively, vs. no emollient, $P < 0.0001$).

Dryness score, extracted from PO-SCORAD, remained constant throughout the study duration in the no emollient group, but a robust decrease was observed in both the V0034CR and reference emollient groups (Fig. 3c). This diminution of the dryness score was visible from the first week of treatment and was maintained over time up to the end of the 12-week treatment period ($P < 0.0001$). After 12 weeks of treatment, a 1.24-point decrease was observed in the V0034CR group, and a 0.88-point

Table 1 Baseline patient characteristics for the full analysis set

	No emollient <i>n</i> = 108	Reference emollient <i>n</i> = 116	V0034CR <i>n</i> = 111	Total <i>n</i> = 335
Gender (<i>n</i> , %)				
Male	54 (50.0)	65 (56.0)	42 (37.8)	161 (48.1)
Female	54 (50.0)	51 (44.0)	69 (62.2)	174 (51.9)
Age (years)				
Mean (SD)	4.06 (1.41)	4.02 (1.37)	4.16 (1.32)	4.08 (1.36)
Family history of atopy (<i>n</i> , %)	77 (71.3)	80 (69.0)	82 (73.9)	239 (71.3)
Time since diagnosis of AD (months)				
Mean (SD)	34.2 (20.1)	34.1 (19.6)	33.6 (18.6)	34.0 (19.4)
Atopic symptoms (<i>n</i> , %)	26 (24.1)	28 (24.1)	26 (23.4)	80 (23.9)
Asthma	9 (34.6)	8 (28.6)	10 (38.5)	27 (33.8)
Rhinitis	16 (61.5)	19 (67.9)	17 (65.4)	52 (65.0)
Time since last flare (months)				
Mean (SD)	2.4 (1.6)	2.3 (1.6)	2.4 (1.6)	2.3 (1.6)
Duration for last flare resolution (days)				
Mean (SD)	11.3 (4.3)	12.2 (4.3)	11.1 (4.5)	11.6 (4.4)

AD, atopic dermatitis; BMI, body mass index; SD, standard deviation.

Table 2 Scoring for Atopic Dermatitis (SCORAD) and objective SCORAD scores evaluated by the investigator: change from baseline at each planned visit for the full analysis set

	No emollient <i>n</i> = 108	Reference emollient <i>n</i> = 116	V0034CR <i>n</i> = 111
SCORAD score (LSM (SE))			
Week 4	5.35 (0.759)	1.38 (0.729)***	−0.96 (0.743)***
Week 8	3.57 (0.790)	−1.35 (0.739)***	−1.80 (0.747)***
Week 12	4.00 (0.808)	−3.36 (0.745)***	−5.28 (0.747)***
Objective SCORAD score (LSM (SE))			
Week 4	3.56 (0.594)	0.06 (0.570)***	−2.00 (0.581)***
Week 8	2.01 (0.618)	−2.15 (0.578)***	−2.79 (0.584)***
Week 12	2.48 (0.632)	−3.80 (0.583)***	−5.48 (0.584)***

LSM, least-square mean; SE, standard error.

****P* < 0.001 vs. 'no emollient' group at each time point.

decrease was observed in the reference emollient group, compared to baseline values (Table 4). At the end of the treatment period, dryness score was reduced significantly in the V0034CR and reference emollient groups compared with the no emollient group (−1.21 and −0.85, respectively, vs. no emollient group, *P* < 0.0001).

As seen with the PO-SCORAD score, the POEM score also increased over the study duration in the no emollient group (Fig. 3d). In contrast, a continuous decrease was observed from week 1 to week 12 in the V0034CR and reference emollient groups (*P* < 0.0001). After 12 weeks of treatment, 4.20-point and 3.03-point decreases from baseline were observed in the V0034CR and reference emollient groups, respectively (Table 4). At the end of the treatment period, the POEM score was reduced by 5.13 points in the V0034CR group and by 3.96

points in the reference emollient group (*P* < 0.0001 vs. no emollient).

Complete remission

After 8 weeks of treatment, the percentage of patients with complete remission was 63.1% for V0034CR and 51.3% for reference emollient (vs. 41.3% for no emollient group; Fig. 4). This difference was statistically significant for both V0034CR (*P* < 0.001) and for reference emollient (*P* = 0.043) compared with the no emollient group.

At the end of the 12-week treatment period, the percentage of patients in complete remission was statistically significantly higher in the V0034CR group (59.5%, *P* < 0.0001) and in the reference emollient group (44.3%, *P* = 0.003) than in the no emollient group (29.8%).

Discussion

The efficacy of emollient creams in reducing xerosis in children with AD has been described previously described.²⁵ Importantly, treating xerosis improves quality of life in these patients²⁶ and reduces flares as well as topical corticosteroid consumption.¹⁵ In agreement with these observations, the use of emollient creams is recommended by treatment guidelines.^{12–14}

In this randomized study, the effects of two emollient creams were assessed in children with mild-to-moderate AD. Primary efficacy results, measured at study completion (i.e. after 12 weeks of treatment), have been already published elsewhere and demonstrated that the regular use of an emollient prevents flares in children with AD.¹⁵ In the present report, we analysed the kinetics of the response over 12 weeks of treatment with these two emollients.

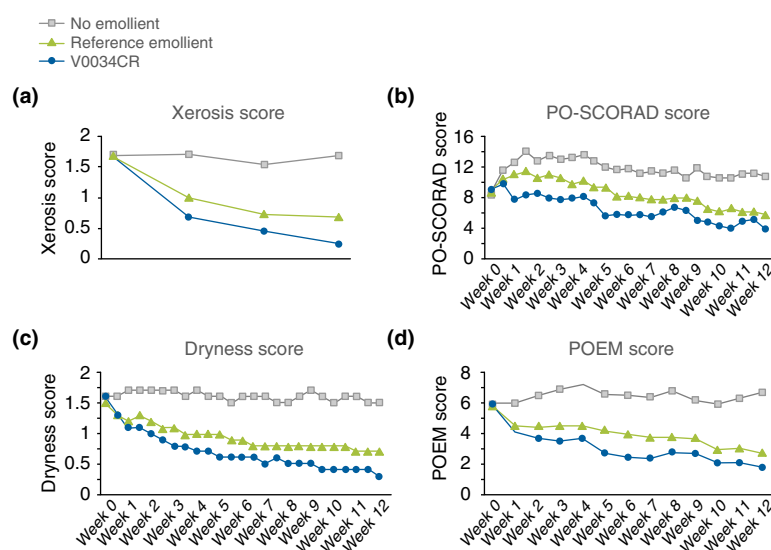


Figure 3 Evaluation of atopic dermatitis symptoms during the treatment period. (a) Xerosis score (i.e. part of the SCORAD score) was evaluated by the investigator at each planned visit. (b) PO-SCORAD, (c) dryness (i.e. part of the PO-SCORAD score) and (d) POEM scores were evaluated by parents either once (POEM) or twice (dryness and PO-SCORAD) a week, over the 12-week treatment period. Patients were either treated with reference emollient ($n = 116$), V0034CR ($n = 111$) or no emollient ($n = 108$). POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis; PO-SCORAD, Patient-Oriented SCORAD. $P < 0.001$ for the V0034CR and reference emollient groups vs. the no emollient group.

Table 3 Pruritus and sleep loss scores: change from baseline at each planned visit for the full analysis set

	No emollient $n = 108$	Reference emollient $n = 116$	V0034CR $n = 111$
Pruritus score (LSM (SE))			
Week 4	1.18 (0.137)	0.85 (0.132)	0.59 (0.134)**
Week 8	1.10 (0.142)	0.53 (0.134)**	0.58 (0.190)**
Week 12	1.00 (0.146)	0.29 (0.135)***	0.10 (0.135)***
Sleep loss score (LSM (SE))			
Week 4	0.56 (0.100)	0.45 (0.096)	0.40 (0.098)
Week 8	0.39 (0.104)	0.23 (0.097)	0.35 (0.098)
Week 12	0.45 (0.106)	0.13 (0.098)*	0.05 (0.098)**

LSM, least-square mean; SE, standard error.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. 'no emollient' group at each time point.

This study clearly showed that the regular use of an emollient progressively and significantly reduces xerosis and improves POEM, SCORAD and PO-SCORAD scores, whereas these scores remained unchanged over the 3-month study duration in children who did not receive emollient treatment (i.e. control group). Interestingly, these effects were already visible after 1 week of treatment, and a continuous reduction in these scores was observed over the 12-week treatment period. It is noteworthy to mention that the double evaluation of AD severity, made either by the physicians (xerosis and SCORAD scores) or by the

Table 4 Dryness, Patient-Oriented Scoring Atopic Dermatitis (PO-SCORAD) and Patient-Oriented Eczema Measure (POEM) scores evaluated by parents: change from baseline at each theoretical week corresponding to planned visits for the full analysis set

	No emollient $n = 108$	Reference emollient $n = 116$	V0034CR $n = 111$
Dryness score (LSM (SE))			
Week 4	0.15 (0.065)	-0.51 (0.060)***	-0.83 (0.061)***
Week 8	-0.03 (0.066)	-0.76 (0.062)***	-1.06 (0.063)***
Week 12	-0.03 (0.808)	-0.88 (0.063)***	-1.24 (0.065)***
PO-SCORAD score (LSM (SE))			
Week 4	5.13 (0.788)	1.53 (0.730)***	-0.75 (0.743)***
Week 8	3.49 (0.814)	-0.60 (0.750)***	-2.01 (0.761)***
Week 12	2.90 (0.824)	-2.67 (0.757)***	-4.88 (0.784)***
POEM score (LSM (SE))			
Week 4	1.37 (0.333)	-1.36 (0.310)***	-2.36 (0.318)***
Week 8	0.93 (0.342)	-2.14 (0.316)***	-3.26 (0.322)***
Week 12	0.93 (0.348)	-3.03 (0.322)***	-4.20 (0.321)***

LSM, least-square mean; SE, standard error.

*** $P < 0.001$ vs. 'no emollient' group at each time point.

parents (PO-SCORAD and POEM scores), is perfectly concordant. Despite the fact that no statistical analyses were planned, and therefore not performed, to compare the effects of the two emollients, these results clearly show that continuous treatment with an emollient is required to provide a clinical benefit. These

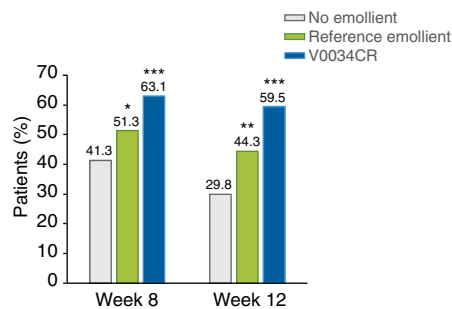


Figure 4 Percentage of patients in complete remission at weeks 8 and 12. Percentage of patients without flare for at least 8 weeks and without anti-inflammatory treatment (i.e. complete remission) was determined in the no emollient ($n = 108$), reference emollient ($n = 116$) and V0034CR ($n = 111$) groups. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. the no emollient group.

observations are in line with a previously published study which showed that stopping emollient treatment results in a relapse of AD, but improvement was observed when emollient treatment was restarted.²⁵

Importantly, the reduction in xerosis and the improvement in AD severity are accompanied by a significant increase in the proportion of patients in complete remission. This effect was significant after 8 weeks of treatment. At the end of the study (i.e. after 12 weeks of treatment), the percentage of patients in complete remission had decreased in both emollient groups compared to week 8 but, interestingly, the difference between the groups became larger. Overall, at study completion, almost 30% of children not receiving emollient were in complete remission compared to 60% of those who received V0034CR.

In conclusion, this study demonstrates that the regular use of an emollient in children with AD not only reduces xerosis but also symptom severity. These results provide support for the regular use of emollients as a first-line treatment in children with mild-to-moderate AD.

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