ORIGINAL ARTICLE

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Prevention of Flares in Children with Atopic Dermatitis with Regular Use of an Emollient Containing Glycerol and Paraffin: A Randomized Controlled Study

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Abstract

Background/Objectives: Emollients are part of the standard treatment for atopic dermatitis (AD), although there is limited evidence that regular use of emollients as management therapy reduces the frequency of flares and corticosteroid consumption. The objective of this study was to evaluate the benefit of emollient use in the management of mild to moderate AD in children by assessing the ability of two different emollients (particularly V0034CR) to prevent flares and to reduce the use of corticosteroids.

Methods: In this randomized, open-label study, patients with a current flare were treated with a potent topical corticosteroid. After flare resolution, patients were centrally randomized to V0034CR emollient, reference emollient, or no emollient (1:1:1 ratio) for 12 weeks. New flares were medically assessed before being treated with a moderately potent corticosteroid.

Results: A total of 335 children 2 to 6 years of age were randomized. At 12 weeks, the percentage of patients with one or more flares was statistically significantly lower with V0034CR (35.1%) than without emollient (67.6%; $p < 0.001$). Fewer patients treated with V0034CR required any corticosteroids or immunosuppressants (23.6%) than patients with no emollient (43.3%) at 12 weeks. The difference was significant at all time points ($p = 0.002$). Patients treated with emollients had a longer time to first flare, fewer flares, higher complete remission rates, less corticosteroid consumption, lower Investigator Global

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Assessment scores, and lower Scoring Atopic Dermatitis scores than those who were not. V0034CR was well tolerated, with no specific safety concerns.
Conclusion: Regular emollient use in children with mild to moderate AD reduces flares and corticosteroid consumption.

Atopic dermatitis (AD) is a chronic or relapsing inflammatory skin disease characterized by xerosis, pruritus, and eczematous lesions (1–4) with periods of acute worsening and flares alternating with periods of relative quiescence after treatment (5). Age at onset is commonly 3 to 6 months, with approximately 60% of patients developing AD in their first year and 90% by 5 years (6).

AD has a complex pathogenesis involving genetic, immunologic, and environmental factors and is associated with epidermal barrier dysfunction. This dysfunction leads to water loss through the skin and generates xerosis, in addition to contributing to allergen and irritant skin penetration, triggering cutaneous inflammation (3,7–9).

The main AD management goals include preserving and restoring barrier function, eliminating inflammation and infection, and controlling exacerbating factors (3,10) to reduce flare occurrence (the burden of this disease). Maintenance emollient therapy with intermittent topical corticosteroid use to treat flares has become standard disease management, but evidence is limited that control of skin hydration and skin barrier function with emollients as maintenance therapy can reduce or delay flares and reduce corticosteroid use (11–13).

This study aimed to evaluate the benefit of emollient use in the management of mild to moderate AD in children. The ability of two different emollients to prevent flares and reduce corticosteroid use after treatment of a previous flare with a topical corticosteroid was assessed.

MATERIALS AND METHODS

This was an international, multicenter, randomized, parallel-group, open-label study in children 2 to 6 years of age with mild to moderate AD diagnosed according to the U.K. Working Party criteria (EudraCT number 2012-004621-24) (14).

Eligible patients had one or more duly documented flares treated with corticosteroids within 6 months of inclusion and a current mild to moderate flare with an objective Scoring Atopic Dermatitis (SCORAD, range 0–83) score of 15 to 40 (grade 3) (15). Patients presenting with any of the following were excluded: other chronic eczema; bacterial, viral, fungal, or parasitic skin infection; ulcerated lesions, acne, or rosacea; other dermatologic diseases that could interfere with assessment; immunosuppression; history of serious disease; oral corticosteroid or immunosuppressant use (within 14 days); or topical corticosteroid, systemic or local antibiotic, nonsteroidal antiinflammatory drug, or antihistamine use (within 7 days).

The study was performed at 27 centers in five countries (France, Estonia, Lithuania, Poland, Romania) in accordance with Good Clinical Practice and approved by the corresponding ethics committees. Parents provided written informed consent for their children's participation.

Study Design

At inclusion, patients were treated for their current flare with a 0.1% desonide potent topical corticosteroid (Locatop, Pierre Fabre Dermatologie Boulogne, 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 SCORAD score less than 15; no lichenification, excoriation, oozing, crusts, edema, papulation, pruritus, or sleep disorders (<1 on the SCORAD visual analog scale); and erythema intensity of 1 or less (with residual erythema area ≤10% of extent). Xerosis was to remain present with an intensity of 1 (mild) or greater.

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

Treatments were applied according to the product monographs. V0034CR (Dexeryl, Pierre Fabre Médicament Boulogne, France) containing glycerol 15% and 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, UK) was applied three times daily to areas of the skin affected or usually or previously affected by AD (16,17).

During treatment, the investigator confirmed flares, which were treated (after medical evaluation and centralized notification through the interactive voice response system) with a 0.1% desonide moderately potent topical corticosteroid (Locapred, Pierre Fabre Dermatologie) once daily until complete resolution.

Primary Efficacy Outcome Measure

The primary outcome measure was determined after 12 weeks of treatment. The investigator assessed the primary efficacy as the percentage of patients with one or more flares. A flare was defined as at least one of the following conditions assessed by the investigator: measurable increase in lesions (extent and intensity) occurring within less than 2 weeks, significant increase (>25%) in AD severity evaluated using the SCORAD (15,18) or the last patient-oriented SCORAD (19,20), and clinical need for topical corticosteroid treatment. Patients who withdrew prematurely for inefficacy of treatment, worsening, unknown or missing reasons, or loss to follow-up were also considered as having a flare (i.e., failures). Two separate flares were recorded if topical corticosteroid use was interrupted for 7 days or more.

Other Endpoints

Secondary outcome measures included time to first flare; time to complete remission (≥8 wks without a flare or antiinflammatory drugs); number of flares; the percentage of patients needing topical corticosteroids or immunosuppressants at 4, 8, and 12 weeks; and corticosteroid consumption. Flare severity was scored using the Investigator Global Assessment (IGA) (range 0 [clear] to 5 [very severe]) (21).

The different SCORAD scores and subcomponents (xerosis, pruritus and sleep loss scores), patient-oriented SCORAD scores, dryness scores, and Patient-Oriented Eczema Measure (POEM) scores (quality of life assessment) (22) were analyzed along with an overall treatment assessment by parents at week 12.

Safety was evaluated by recording adverse events (AEs). All AEs that occurred or worsened after randomization were considered treatment-emergent AEs (TEAEs).

Statistical Analysis

Statistical analyses (efficacy and safety) were performed using SAS version 9.3 (SAS Institute, Cary, NC) on the full analysis set, comprising all randomized treated patients. Supportive efficacy analysis on the primary endpoint was performed on the per protocol set, comprising patients from the full analysis set with no major protocol deviations.

The primary efficacy outcome of V0034CR and no emollient groups (20 percentage points expected between-group difference) was compared using a Cochran–Mantel–Haens zel (CMH) test stratified according to pooled centers with modified ridit score. Post hoc analysis of the primary endpoint evaluated the effect of sex using a CMH test.

Secondary efficacy endpoints were analyzed using the Kaplan–Meier method with a log-rank test, CMH stratified according to center, CMH stratified according to center with modified ridit score, or a mixed-effects model for repeated measurements. Hazard ratios and 95% confidence intervals were estimated using the Cox regression model. Safety was analyzed using descriptive statistics.

The necessary sample size was estimated to be 327 patients (109 per group) to achieve a 90% 1–β power with a type 1 error set α at 5% (two sided), assuming that the percentage of patients in each group with at least one flare would be 20% for each emollient and 40% for no emollient.

RESULTS

Patients were included between February and March 2013 and between September and November 2013, with the first patient enrolled on February 7, 2013. Of a total of 347 children included, 335 were randomized, 316 completed, and 19 were withdrawn (most frequently for efficacy concerns [n = 9]) (Fig. 1). Of the 335 patients, 111 were randomized to V0034CR, 116 to reference emollient, and 108 to no emollient; all were included in the full analysis set.

More girls (62.2%) were randomized to V0034CR and more boys to reference emollient (56.0%). Other patient characteristics were similar across the three groups (Table 1): mean age was 4.1 years, mean time since AD diagnosis was 34.0 months, and mean objective SCORAD score ranged from 30.5 to 31.6. At inclusion, flare severity was moderate or mild (IGA = 3 or 2) in almost all patients (74.0% and 23.6%), and at randomization, all flares were clear or almost clear (IGA = 0 or 1). Adherence to V0034CR was good for all patients except one.

EFFICACY

Primary Endpoint

Over 12 weeks of treatment, the percentage of patients with one or more flares was statistically

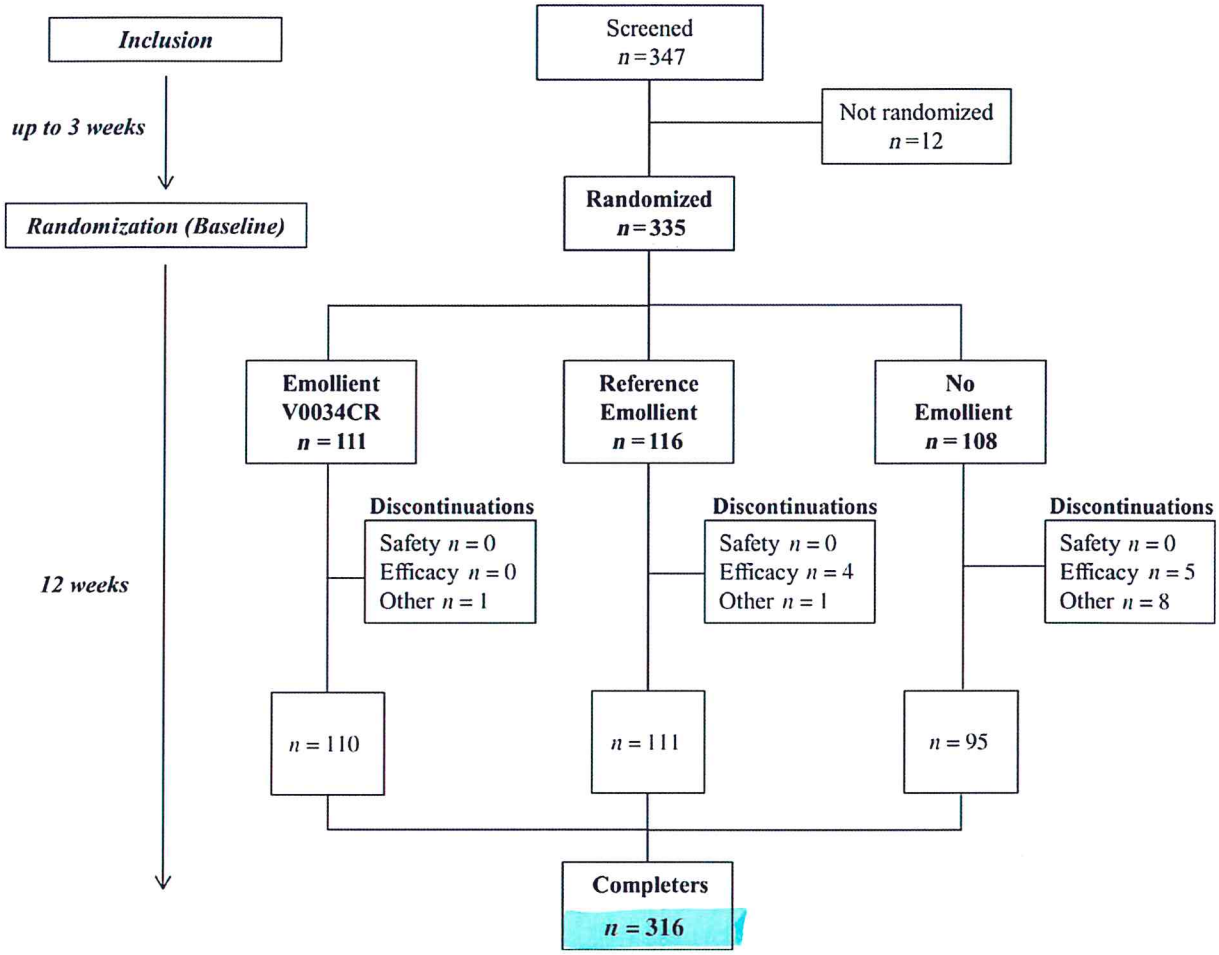

Figure 1. Flow chart of overall study population.

TABLE 1. *Baseline Patient Characteristics for the Full Analysis Set*

Characteristic	V0034CR (n = 111)	Reference emollient (n = 116)	No emollient (n = 108)	Total (n = 335)
Sex, n (%)				
Male	42 (37.8)	65 (56.0)	54 (50.0)	161 (48.1)
Female	69 (62.2)	51 (44.0)	54 (50.0)	174 (51.9)
Age, years, mean ± SD	4.2 ± 1.3	4.0 ± 1.4	4.1 ± 1.4	4.1 ± 1.4
Family history of atopy, n (%)	82 (73.9)	80 (69.0)	77 (71.3)	239 (71.3)
Atopic symptoms, n (%)	26 (23.4)	28 (24.1)	26 (24.1)	80 (23.9)
Asthma	10 (38.5)	8 (28.6)	9 (34.6)	27 (33.8)
Rhinitis	17 (65.4)	19 (67.9)	16 (61.5)	52 (65.0)
Time between diagnosis of AD and randomization, months, mean ± SD	33.6 ± 18.6	34.1 ± 19.6	34.2 ± 20.1	34.0 ± 19.4
Time between last flare and inclusion, months, mean ± SD	2.4 ± 1.6	2.3 ± 1.6	2.4 ± 1.6	2.3 ± 1.6
Corticosteroids used for treating last flare before inclusion, n (%)	111 (100)	115 (99.1)	106 (98.1)	332 (99.1)
Duration of last flare resolution, days, mean ± SD*	11.1 ± 4.5	12.2 ± 4.3	11.3 ± 4.3	11.6 ± 4.4

*Between inclusion and randomization, corresponding to treatment with Locatop.
AD, atopic dermatitis; SD, standard deviation.

significantly lower ($p < 0.001$) with V0034CR (35.1%) than without emollient (67.6%). The between-group difference of 32.5 percentage points was greater than the hypothesized 20 percentage points. Supportive analysis in the per protocol set confirmed these results (36.7% vs 72.2%; $p < 0.001$). Post hoc analysis showed that the uneven sex ratio in the V0034CR group did not affect the primary efficacy results; the percentage of patients with one or more flares was statistically significantly lower ($p < 0.001$) with V0034CR than without emollient for boys (31.0% vs 68.5%) and girls (37.7% vs 66.7%).

Secondary Endpoints

The percentage of patients with one or more flares was statistically significantly lower with reference emollient (52.6%) than no emollient (67.6%) ($p = 0.004$). The time to first flare after randomization was statistically significantly shorter without emollient than with each emollient (V0034CR, $p < 0.001$; reference emollient, $p = 0.009$) (Fig. 2). Fewer flares were experienced over 12 weeks with both emollients (Table 2).

At 12 weeks, 59.5% of patients using V0034CR, 44.3% using the reference emollient, and 29.8% without emollient were in complete remission. The difference was statistically significant between no emollient and both emollient groups (V0034CR, $p < 0.001$; reference emollient, $p = 0.003$).

Fewer patients treated with V0034CR required topical corticosteroids or immunosuppressants (23.6%) than those without emollient (43.3%) at 12 weeks. The difference was significant at all time points ($p \leq 0.002$). Results were similar for the reference emollient, with significant differences at 8 and 12 weeks ($p \leq 0.03$). The percentage of days that corticosteroids were applied over 12 weeks is presented in Table 3; 64.9% of those who used V0034CR, 47.4% of those who used the reference emollient and 36.1% of those who used no emollient did not use corticosteroids. Overall, the difference in corticosteroid use was statistically significant between the no emollient group and both emollient groups (V0034CR, $p < 0.001$; reference emollient, $p < 0.001$).

For other secondary endpoints that investigators (different SCORAD scores and subcomponents) or parents (patient-oriented SCORAD, POEM, dryness score) evaluated, baseline scores were similar, but 12-week changes were significantly different between no emollient and V0034CR or reference emollient scores ($p = 0.01$ for sleep loss; $p < 0.001$ for all other scores) (Table S1).

After 12 weeks, 77.3% of patients using V0034CR, 70.3% using the reference emollient, and 53.1% using no emollient had no inflammatory AD signs (IGA

TABLE 2. *Number of Flares According to Treatment Group*

Number of flares during study	V0034CR ($n = 111$), n (%)	Reference emollient ($n = 116$), n (%)	No emollient ($n = 108$), n (%)
0	72 (64.9)	55 (47.4)	35 (32.4)
1	28 (25.2)	44 (37.9)	47 (43.5)
2	9 (8.1)	16 (13.8)	20 (18.5)
3	2 (1.8)	1 (0.9)	3 (2.8)
≥4	0	0	3 (2.8)

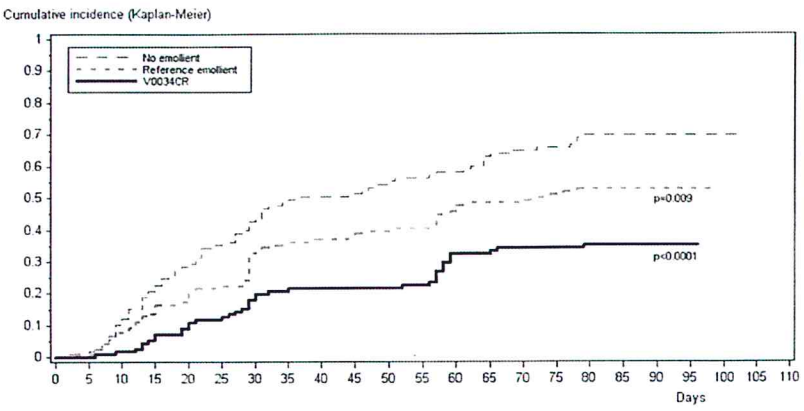

Figure 2. Comparison of cumulative incidence of time to first flare according to treatment group analyzed on the full analysis set. The time to first flare was statistically significantly shorter without emollient than with V0034CR ($p < 0.001$) or reference emollient ($p = 0.009$).

TABLE 3. *Percentage of Days of Corticosteroid Use*

	V0034CR (n = 111)	Reference emollient (n = 116)	No emollient (n = 108)
Percentage of days of corticosteroid use, n (%)			
0	72 (64.9)	55 (47.4)	39 (36.1)
0–10	16 (14.4)	32 (27.6)	12 (11.1)
10–20	15 (13.5)	17 (14.7)	29 (26.9)
20–40	7 (6.3)	10 (8.6)	18 (16.7)
>40	1 (0.9)	2 (1.7)	10 (9.3)
Cochran–Mantel–Haenszel p-value stratified according to pooled center versus no emollient	<0.001	<0.001	

clear). Parents reported a global opinion of treatment as very good in 79.1% of cases with V0034CR versus 38.6% with the reference emollient.

Safety

In total, 231 patients (69%) experienced 375 TEAEs (Table 4); the frequency was lower in the V0034CR (62.2%) and reference emollient (66.4%) groups than the no emollient group (73.1%). Other than flare (AE reporting required per protocol for homogeneity), which led to discontinuation of seven patients, the most frequently reported TEAEs were bronchitis, nasopharyngitis, and rhinitis, with a similar percentage of patients in each group.

The investigator assessed 11 TEAEs as treatment related. Almost all AEs were mild or moderate in severity; seven were severe. Four patients experienced five serious AEs (not treatment related).

DISCUSSION

This randomized, open-label study analyzed the effects of two emollients (particularly V0034CR) in the treatment of children with AD and aimed to validate emollient use as a therapeutic approach for AD management. The study sample was representative of the population of children with mild to moderate AD.

No treatment was chosen as the negative control since placebo use could potentially affect xerosis. A reference emollient of well-established efficacy was used as an active control to ensure the sensitivity of the study (23,24.) Because of the different aspects and application conditions of the emollients and the presence of a no-emollient group, a double-blind study design was not possible, but patients were centrally randomized to prevent bias in the study population. Statistical comparison between the two emollients was not planned; V0034CR and reference emollient were compared with no emollient.

Primary efficacy endpoint analysis showed that the percentage of patients with one or more flares was statistically significantly lower with V0034CR (35.1%) than no emollient (67.6%), and supportive analyses confirmed the robustness of this result. Overall, the difference in the percentage of patients with flares was of clinical relevance, with a frequency in V0034CR-treated patients half that of patients without emollient. The effect on the quality of life measured using the POEM score corroborated this result.

Patients treated daily with emollients used fewer corticosteroids. Few previous studies have demonstrated that regular emollient use in AD treatment can affect corticosteroid consumption (11–13). Although

TABLE 4. *Summary of Adverse Events (AEs)*

	V0034CR (n = 111)		Reference emollient (n = 116)		No emollient (n = 108)	
AEs	Events, n	Patients, n (%)*	Events, n	Patients, n (%)*	Events, n	Patients, n (%)*
All AEs	127	71 (64.0)	138	80 (69.0)	138	80 (74.1)
All TEAEs	117	69 (62.2)	126	77 (66.4)	132	79 (73.1)
Condition aggravated		40 (36.0)		61 (52.6)		72 (66.7)
Nasopharyngitis		8 (7.2)		5 (4.3)		7 (6.5)
Bronchitis		7 (6.3)		9 (7.8)		8 (7.4)
Rhinitis		7 (6.3)		2 (1.7)		3 (2.8)
AE leading to definitive investigational product or study discontinuation	0	0 (0.0)	4	4 (3.4)	3	3 (2.8)
Related TEAE	1	1 (0.9)	9	8 (6.9)	1	1 (0.9)
Serious AEs	2	2 (1.8)	1	1 (0.9)	2	1 (0.9)
Related serious AEs	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

Related treatment-emergent AEs (TEAEs) were events with suspected causality related to the product or with insufficient data. TEAEs occurred in >5% patients.
*Patients with at least one event. A given patient may have reported more than one AE, so numbers in columns cannot be added.

topical corticosteroids are first-line treatment for AD flares, prolonged application can lead to skin atrophy, among other complications (3). Systemic absorption of high-potency agents may result in adrenal suppression and growth retardation in children (25,26).

V0034CR was well tolerated over 12 weeks, with no particular safety concerns. Daily emollient use in children with mild to moderate AD led to a decrease or delay of flares and reduced corticosteroid consumption. Regular emollient use as maintenance therapy for mild to moderate AD results in better patient care.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Change from Baseline to 12 weeks of Xerosis, Pruritus, Sleep score, SCORAD, Objective SCORAD and PO-SCORAD.

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

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Running short title: Regular emollient use improves AD symptoms

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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 of AD severity in children with AD.

Methods: In this multicenter 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 (SCORAD and subcomponents, IGA) and by parents (PO-SCORAD and POEM).

Results: 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.

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]

AD flares are usually treated with topical corticosteroids in order 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% versus 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, multicenter, 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 centers across 5 countries (France, Estonia, Lithuania, Poland, 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) 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, edema, papulation, pruritus or sleep disorders (<1 on the SCORAD Visual Analog 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, 18, 19], They were applied according to the product monographs. V0034CR (Dexeryl®, Pierre Fabre Médicament), containing glycerol 15%, liquid and soft paraffin 10%, was applied twice daily (8g per application) to the whole body (and face). The reference emollient (Atopiclair®, Sinclair Pharma) was applied three times daily to areas of the skin affected, or usually/previously affected, by AD.

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 eczema; 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) score, [24] 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 of lesions (extent/intensity) occurring within less than 2 weeks; significant increase (>25%) in AD severity evaluated by the SCORAD or PO-SCORAD; 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).

The percentage of patients with complete remission was compared between active groups versus the no emollient group using a CMH test stratified by center (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, center 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 analyzed 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 and objective 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 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 ($p<0.0001$ versus 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, versus 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 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, versus 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 (versus 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 patients, [26] 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 analyzed the kinetics of the response over 12 weeks of treatment with these two emollients.

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 of 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 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 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 of 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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FIGURE and TABLE LEGENDS

Figure 1. Study design.

Figure 2. Patient flow chart.

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). SCORAD: Scoring Atopic Dermatitis; PO-SCORAD: Patient Oriented SCORAD; POEM: Patient Oriented Eczema Measure. $p<0.001$ for the V0034CR and reference emollient groups versus the no emollient group.

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. *$p<0.05$, **$p<0.01$, ***$p<0.001$ versus the no emollient group.

Table 1. Baseline patient characteristics for the full analysis set.

Table 2. SCORAD and Objective SCORAD scores evaluated by the investigator: change from baseline at each planned visit for the full analysis set.

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

Table 4. Dryness, PO-SCORAD and POEM scores evaluated by parents: change from baseline at each theoretical week corresponding to planned visits for the full analysis set.

Table 1. Baseline patient characteristics for the full analysis set.

	No emollient n=108	Reference emollient n=116	V0034CR n=111	Total n=335
Gender (n, %)				
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 (n, %)	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 (n, %)	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. SCORAD and Objective SCORAD scores evaluated by the investigator: change from baseline at each planned visit for the full analysis set.

	No emollient n=108	Reference emollient n=116	V0034CR n=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 versus "no emollient" group at each time-point

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 versus "no emollient" group at each time-point

Table 4. Dryness, PO-SCORAD and 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 versus "no emollient" group at each time-point

Figure 1

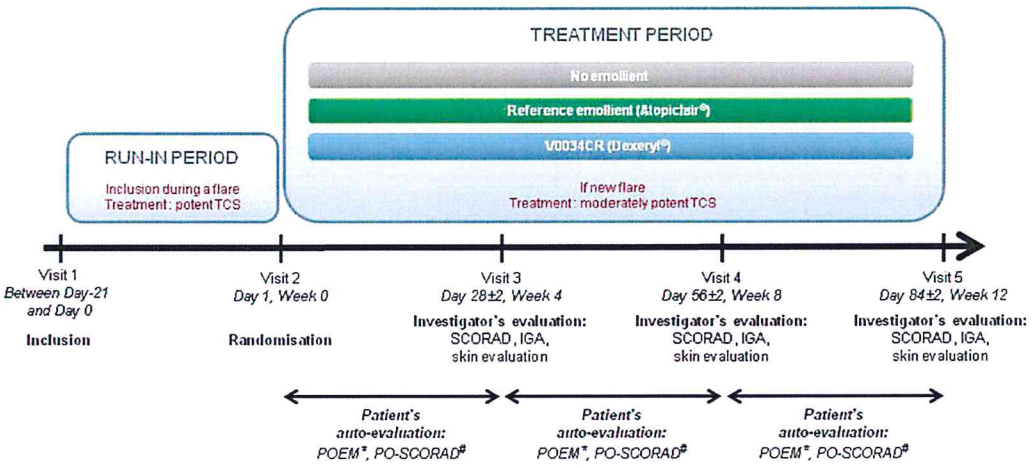
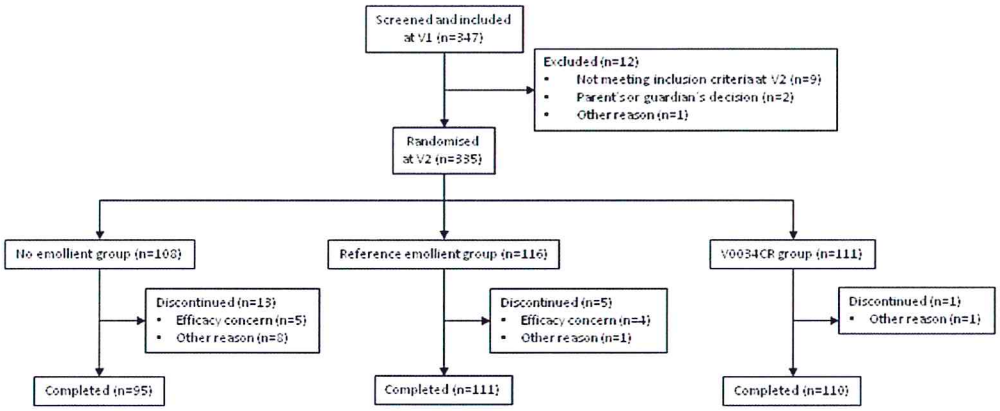


Figure 2



	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 3

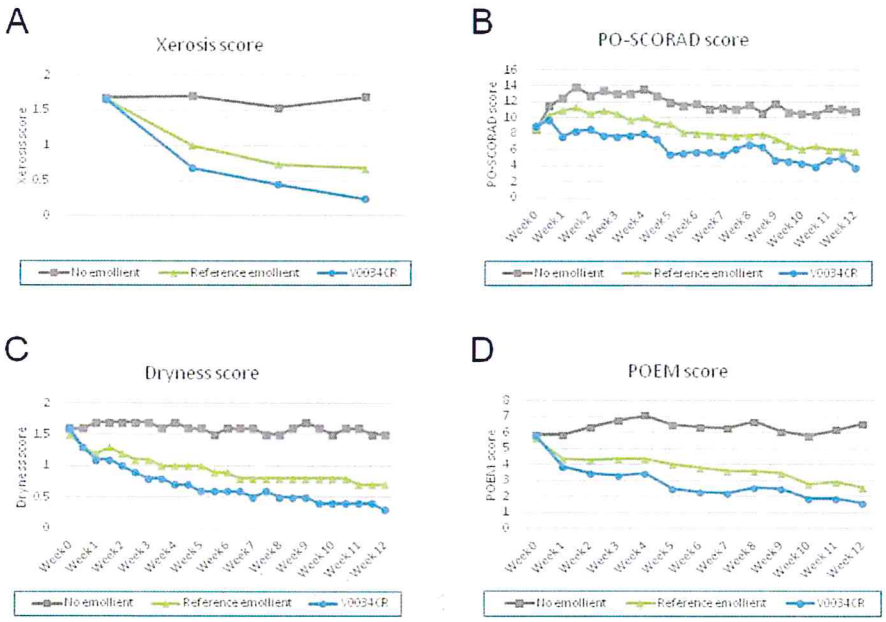
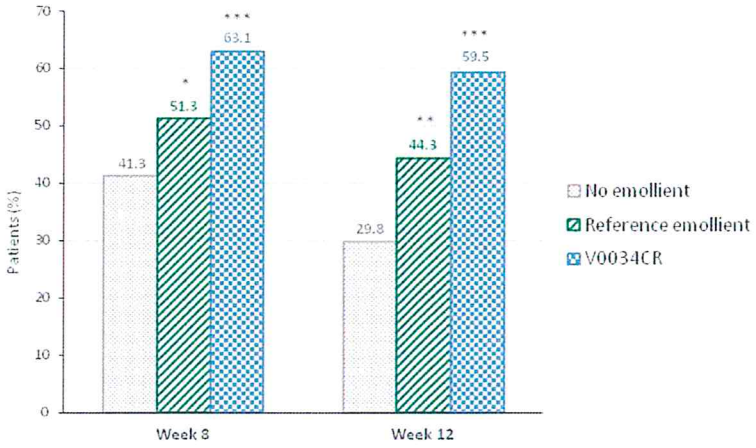


Figure 4



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