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ORIGINAL RESEARCH

Severity of Local Skin Reactions with 4% 5-Fluorouracil Plus Emollient versus 4% 5-Fluorouracil Alone in Patients with Actinic Keratosis: A Single-Blind Randomised Trial

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ABSTRACT

Introduction: Topical 5-fluorouracil (5-FU)-containing treatments are effective for actinic keratosis (AK); however, they frequently lead to transient local skin reactions (LSRs), which often result in treatment non-adherence.
Methods: The aim of this international, phase IV clinical trial was to investigate whether addition of an emollient to topical 4% 5-FU would reduce the frequency and severity of LSRs over 4 weeks of treatment (intervention group) compared with 4% 5-FU alone (control group) in patients with AK. The primary objective was to assess the severity of LSRs (i.e. erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation and erosion/ulceration) at week 4 of treatment (or before, in case of a major local reaction). Key secondary objectives were LSR total scores at weeks 2 and 8, the scores of individual LSR items at each visit, and the proportions of patients with 100% and ≥ 75% AK lesion clearance at week 8.
Results: In total, 141 patients were included in the efficacy analysis (71 in the intervention group and 70 in the control group). There were no statistically or clinically significant differences between the treatment groups in terms of LSR total score at week 4 (overall and by subgroups defined by the number of lesions and patient age at baseline), scores of individual LSR items at any time point, and AK lesion clearance rates at week 8. LSR scores with topical 4% 5-FU alone were lower than expected. Skin reactions

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were the most common treatment-emergent adverse events in both groups, leading to treatment discontinuation in nine patients (12.3%) in the intervention group and seven (9.9%) in the control group. No new safety signals were observed with the addition of an emollient to 4% 5-FU.

Conclusions: Daily emollient applications during the 4-week treatment course did not impact the safety and efficacy profile of 4% 5-FU.

Keywords: Actinic keratosis; Emollient; Local skin reactions; Topical 5-fluorouracil

Key Summary Points

Why carry out this study?

Topical 5-fluorouracil (5-FU)-containing treatments for actinic keratosis (AK) are frequently associated with transient local skin reactions (LSRs).

This phase IV randomised trial investigated whether treatment with 4% 5-FU plus emollient cream would reduce the severity of LSRs compared with 4% 5-FU alone over 4 weeks in patients with AK.

What was learned from the study?

There was no statistically significant difference in mean LSR total scores at week 4 between patients who received 4% 5-FU plus emollient and those who received 4% 5-FU alone, although addition of emollient showed a possibly clinically favourable effect in patients with <10 lesions at baseline and in those aged ≥80 years.

Skin reactions were the most common treatment-emergent adverse event in both treatment groups, but LSR total scores were lower than expected during topical 4% 5-FU treatment.

The safety and effectiveness of topical 4% 5-FU cream for AK were not significantly modified by addition of emollient.

INTRODUCTION

Actinic keratoses (AKs) are cutaneous lesions resulting from cumulative sun exposure that are characterised by proliferation of atypical epidermal keratinocytes [1, 2]. They typically present as multiple lesions in the form of scaly patches, macules or papules with poorly defined borders, and occasionally appear as thick, adherent scales over an erythematous base [3, 4]. AKs can persist in the same stage or may regress spontaneously (15–63% of lesions per year) or undergo malignant transformation into invasive squamous cell carcinoma (iSCC; 0.1–20% of lesions or up to 0.5% of lesions per year) [1, 5]. The prevalence of AK is 11–25% worldwide [6], and depends on the geographical variability in ultraviolet radiation levels [7]. The highest prevalence of AK is in Australia (40–59%) [8, 9], while the prevalence is generally lower across Europe, affecting 4.7% of individuals in France [10], 11.2–23.0% in the UK [11, 12], 27.4% in Italy [13], 28.6% in Spain [14], 31.0% in Austria [15] and 37.5% in the Netherlands [7].

In patients with AK, the primary treatment goals are the eradication (complete or partial) of lesions, improvement in skin appearance, reduction in pain and other symptoms, increase in disease-free intervals and decrease in the overall risk of malignant progression to iSCC [1, 5]. The choice of treatment is based on the location of the lesions and treatment-related factors, as well as patient characteristics and preferences [1, 2]. Lesion-directed treatment may be used in patients with localised or hyperkeratotic AK lesions, and include cryotherapy, laser treatment or surgery (excision, curettage). Field-directed treatments, such as topical treatments [e.g. 5- fluorouracil (5-FU) in concentrations ranging from 0.5% to 5%, imiquimod (3.75% or 5%), diclofenac sodium (3%), tirbanibulin (1%), 5-aminolevulinic acid and methyl aminolevulinate] with photodynamic therapy (PDT) or daylight, are indicated to treat patients with multiple clinical lesions and underlying field damage [1, 2].

Among the available topical options used for field-directed treatment of AKs, 5-FU-

containing treatments are effective and widely prescribed [16–19]. However, as with most efficient topical treatments for AK, 5-FU-containing treatments frequently lead to transient application site reactions, commonly known as local skin reactions (LSRs) [20], which are considered a normal positive response that is related to the pharmacological action of 5-FU [21].

LSRs may manifest clinically as erythema, scaling/dryness, flaking, oedema, crusting/scabbing, erosions/ulcerations, stinging/burning and pruritus, usually peaking after 4 weeks of treatment and resolving within 2–4 weeks of treatment discontinuation [20, 22, 23]. The most recently developed topical 5-FU preparation (Tolak; Pierre Fabre) is composed of 4% 5-FU in an aqueous cream base that contains peanut oil. In clinical trials of this 4% 5-FU preparation applied once daily (one phase II and one phase III trial), the incidence of LSRs was 62–99% by individual symptoms [20, 22]. LSRs were mild to moderate in 17–44% of patients and severe in 6–38% of patients [20].

Even if severe LSRs are less frequent with 4% 5-FU once daily than with 5% 5-FU twice daily [21], the challenge with topical 5-FU treatment remains to reduce the incidence and/or severity of LSRs and improve local tolerance without interfering with its efficacy. One potential tool for overcoming this challenge is the addition of an emollient during 5-FU treatment. The aim of the current study was to investigate whether treatment with 4% 5-FU (Tolak) plus emollient cream (Glycerol Vaseline Paraffin, Pierre Fabre, France) would reduce the severity of LSRs over 4 weeks compared with 4% 5-FU alone in patients with AK.

METHODS

Study Design

This interventional, single-blind, phase IV, randomised controlled trial was conducted between October 2020 and March 2021 at 22 investigational centres located in Germany, France, Italy and Spain (EudraCT number 2020–000,851-11). The study protocol and documents required by national regulatory authorities were approved by independent ethics committees and health authorities before the start of the study. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments, the International Conference on Harmonisation guidelines for Good Clinical Practice, and related national regulations. All participants voluntarily provided written informed consent prior to any study procedures being undertaken.

Patient Population

Patients with AK were eligible for study inclusion if they were aged ≥ 18 years and had ≥ 5 non-hyperkeratotic, non-hypertrophic AK lesions (Olsen grade I and II) on their face, ears and/or scalp and were free of skin cancer and active dermatological conditions in the treated area. Treatment with corticosteroids, immunosuppressants or immunomodulators within 4 weeks was not permitted. Patients were excluded if they had hyperkeratotic skin lesions or lesions with clinical suspicion for SCC, pre-existing LSRs with a total score ≥ 3, a history of hypersensitivity to the study products or peanut or soya, dihydropyrimidine dehydrogenase deficiency, or if they were pregnant or breast-feeding. Other exclusion criteria included systemic 5-FU or any systemic cancer treatment, any other topical treatments or therapies for AK (e.g. cryotherapy or PDT) or the use of chemical peeling products in the treatment area(s) within 8 weeks, application of retinoids or topical steroids, glycolic acid products and alpha-hydroxy products in the treatment area(s) or treatment with brivudine, sorivudine or analogues within 4 weeks.

Randomisation and Treatment

Patients were randomly allocated (using PCL® software) in a 1:1 ratio to the intervention group, who received 4% 5-FU for 4 weeks plus the emollient cream for 8 weeks, or to the control group, who received 4% 5-FU alone for 4 weeks. Treatments were allocated in a double-blinded manner; however, patients were unblinded by opening the box containing the

treatment. As investigators remained blinded to the treatment allocation, patients were instructed to not reveal their allocation group and avoid discussing the features, dosing frequency or packaging of the study intervention with the investigator. If required, investigators could be unblinded for patient safety reasons.

Treatments were administered once daily according to the summary of product characteristics for 4% 5-FU [20], with application of the emollient in the morning and of 4% 5-FU in the evening (in both treatment arms). Patients attended four clinic visits: at baseline, week 2, week 4 and week 8 (after 4 weeks off active treatment). An optional visit was scheduled in case of a major local reaction before week 4, during which rescue treatment with topical corticosteroids or an emollient (for patients in the control group only) could be initiated. In case of treatment discontinuation, the follow-up visit at week 8 was not required.

Study Objectives

The primary objective was to assess the severity of LSRs at the end of the treatment course. The severity of LSRs was assessed by determining the LSR total score at week 4 (or before, in case of a major local reaction). For the LSR total score, six objective items (erythema, flaking/scaling, crusting, swelling, vesiculation/postulation and erosion/ulceration) were each assessed on a 5-point scale from 0 to 4 (0: none; 1: mild; 2: moderate; 3: moderately severe; and 4: severe), yielding a composite score ranging from 0 (best outcome possible) to 24 (worst outcome possible) [24]. The LSR total score was recorded at each study visit for each patient. Details of the scoring system of the individual LSRs are given in Table S1 in the electronic supplementary material.

The secondary objectives were the overall safety and tolerability, including LSR total score at weeks 2 and 8, individual item LSR scores at each visit and the proportion of patients with severe LSRs at week 4 (i.e. individual item LSR scores of 3 or 4), as well as the proportion of patients with 100% AK clearance [complete clearance rate (cCR)] and $\geq$ 75% lesion clearance [partial clearance rate (pCR)] at week 8.

Treatment-emergent AEs (TEAEs) were defined as the appearance of a new single AE, the reappearance of a previously recovered AE

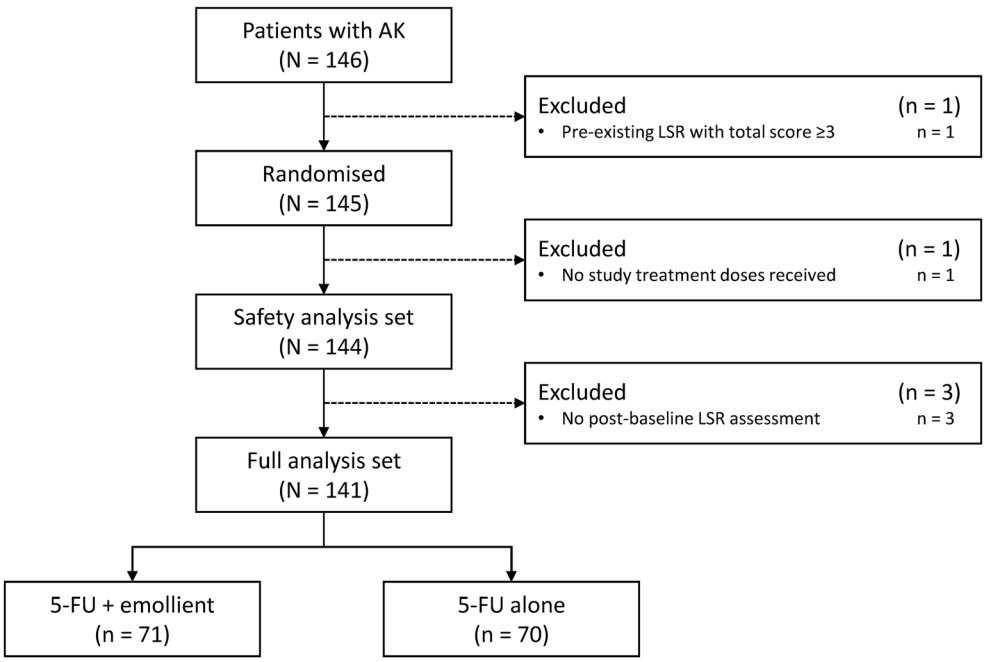


Fig. 1 Disposition of patients in the study. *5-FU* 4% 5-fluorouracil, *AK* actinic keratosis, *LSR* local skin reaction

or the worsening of a continuous event AE (relative to its previous status).

Statistical Analysis

Assuming a 10% premature drop-out or withdrawal rate, a sample size of 140 patients was estimated so that at least 126 evaluable patients would complete the study to show a 3-point difference with 80% power. The full analysis set was composed of all patients assigned to a study treatment who received at least one dose of the study treatment and had at least one evaluation of the primary endpoint post treatment. The LSR total score was also evaluated according to the number of lesions (< 10 or ≥ 10) at baseline. The safety analysis set was composed of all patients randomly assigned to a study treatment and who received at least one dose of the study treatment. Missing values were imputed using the last observation carried forward (LOCF) method for primary and subgroup analyses and for the number of lesions at week 8.

Quantitative parameters were summarised using descriptive statistics, and those without baseline values were compared between groups by a Student's *t*-test or a Wilcoxon test according to the normality/non-normality assumption of the primary analysis. Qualitative parameters were described by treatment group and overall, using frequencies and percentages. They were compared between groups using a chi-squared test or a Fisher's exact test. Ordinal parameters were compared between groups using a Cochran–Mantel–Haenszel test. All statistical analyses were performed at the 0.05 global significance level, using two-sided tests. The statistical analyses were conducted using SAS software (version 9.4).

RESULTS

Patients

In total, 146 patients were screened, 145 fulfilled eligibility criteria and were randomised, and 144 received treatment (safety analysis set). Three patients in the safety analysis set had no post-baseline LSR assessments, therefore, 141 evaluable patients were included in the full analysis set: 71 patients received 4% 5-FU plus emollient (intervention group) and 70 patients

Table 1 Patient baseline characteristics

	4% 5-FU + emollient *n* = 71	**4% 5-FU alone *n* = 70**	**Total *N* = 141**
Age, years			
Mean (SD)	74.1 (7.8)	75.5 (7.1)	74.8 (7.5)
Category, *n* (%)			
18–64 years	7 (9.9)	5 (7.1)	12 (8.5)
65–84 years	61 (85.9)	58 (82.9)	119 (84.4)
≥ 85 years	3 (4.2)	7 (10.0)	10 (7.1)
Sex, *n* (%)			
Male	63 (88.7)	66 (94.3)	129 (91.5)
Female	8 (11.3)	4 (5.7)	12 (8.5)
BMI, kg/m^2			
Mean (SD)	26.3 (4.1)	26.6 (3.7)	26.5 (3.9)
Skin phototype (Fitzpatrick classification), *n* (%)			
I	7 (9.9)	11 (15.7)	18 (12.8)
II	47 (66.2)	46 (65.7)	93 (66.0)
III	17 (23.9)	12 (17.1)	29 (20.6)
IV	0	1 (1.4)	1 (0.7)
Number of lesions			
Mean (SD)	11.4 (6.7)	12.9 (8.9)	12.2
≥ 10 lesions, *n* (%)	35 (49.3)	37 (52.9)	72 (51.1)

5-FU 5-fluorouracil, *BMI* body mass index, *SD* standard deviation

received 4% 5-FU alone (control group) (Fig. 1). The baseline characteristics of the patients were generally well balanced between the treatment groups (Table 1), although the proportion of males and patients with skin phototype I was numerically higher in the control group than in the intervention group. In the full analysis set, the mean age was 74.8 years, the majority of patients were male (91.5%) and the most prevalent skin phototype was type II (66.0%). The mean AK lesion count at baseline was 12.2 and 51.1% of patients had ≥ 10 lesions.

In the safety analysis set, the mean duration of exposure to 4% 5-FU was comparable between the intervention and control groups (25.7 and 26.9 days, respectively). The number of patients with < 20 days' exposure was higher in the intervention group than in the control group (13 versus 7 patients, respectively).

Of the 145 patients randomised, 28 patients (19.3%) discontinued treatment (18 patients in the intervention group and 10 in the control group). The main reason for study discontinuation was AE [17 patients (13.9%), including 10 (13.5%) in the intervention group and 7 (9.9%) in the control group]. Other reasons were withdrawal by patient [seven patients (4.8%), including five (6.8%) in the intervention group and two (2.8%) in the control group] and non-compliance with study intervention [three patients (2.1%), including two (2.7%) and one (1.4%) patient in the respective groups]; one patient (0.7%) in the intervention group withdrew due to stress for personal reasons.

LSR Severity

At baseline, the mean LSR total score was 1.6 in both the intervention and the control groups (Fig. 2). At week 4, the mean LSR total score was 7.1 in the intervention group and 7.7 in the control group. The least squares mean (LSM) between-group difference, adjusted for LSR total score at baseline, was −0.55 [95% confidence interval (CI) −1.90, +0.79; $p = 0.4154$], but was not statistically significant. However, the difference in mean LSR total score at week 4 was more in favour of the intervention group in patients with < 10 lesions at baseline (LSM difference −1.51; 95% CI −3.51, +0.49; $p = 0.1371$) than in patients with ≥ 10 lesions at baseline (LSM difference +0.34; 95%

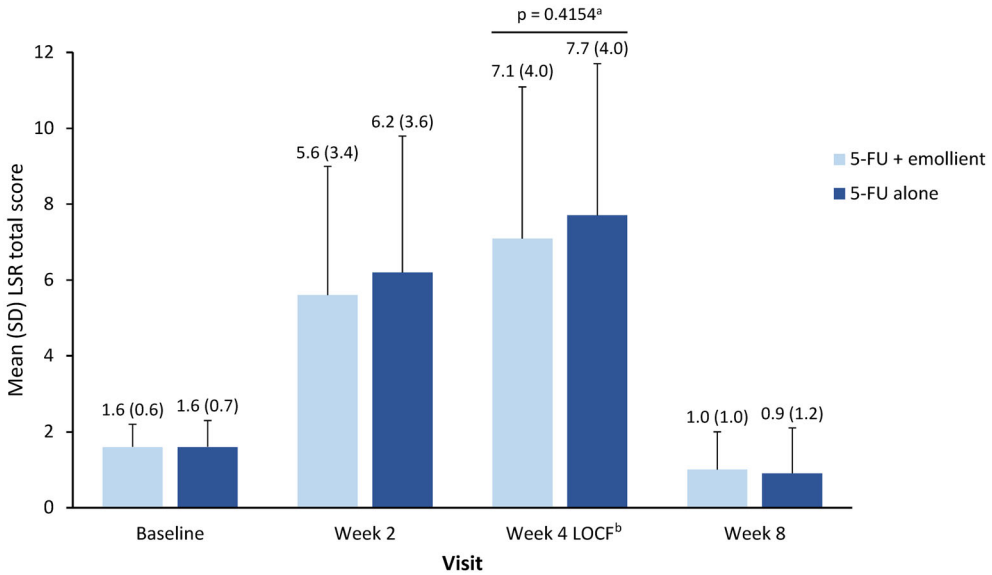


Fig. 2 Local skin reaction total scores during the study among patients receiving 4% 5-FU plus emollient or 4% 5-FU alone (full analysis set). *5-FU* 5-fluorouracil, *LOCF* last observation carried forward, *LSR* local skin reaction, *SD* standard deviation. **a** Two-sided test for treatment effect. **b** LSR score at week 4, or at an optional visit or week 2 in cases of major local reaction

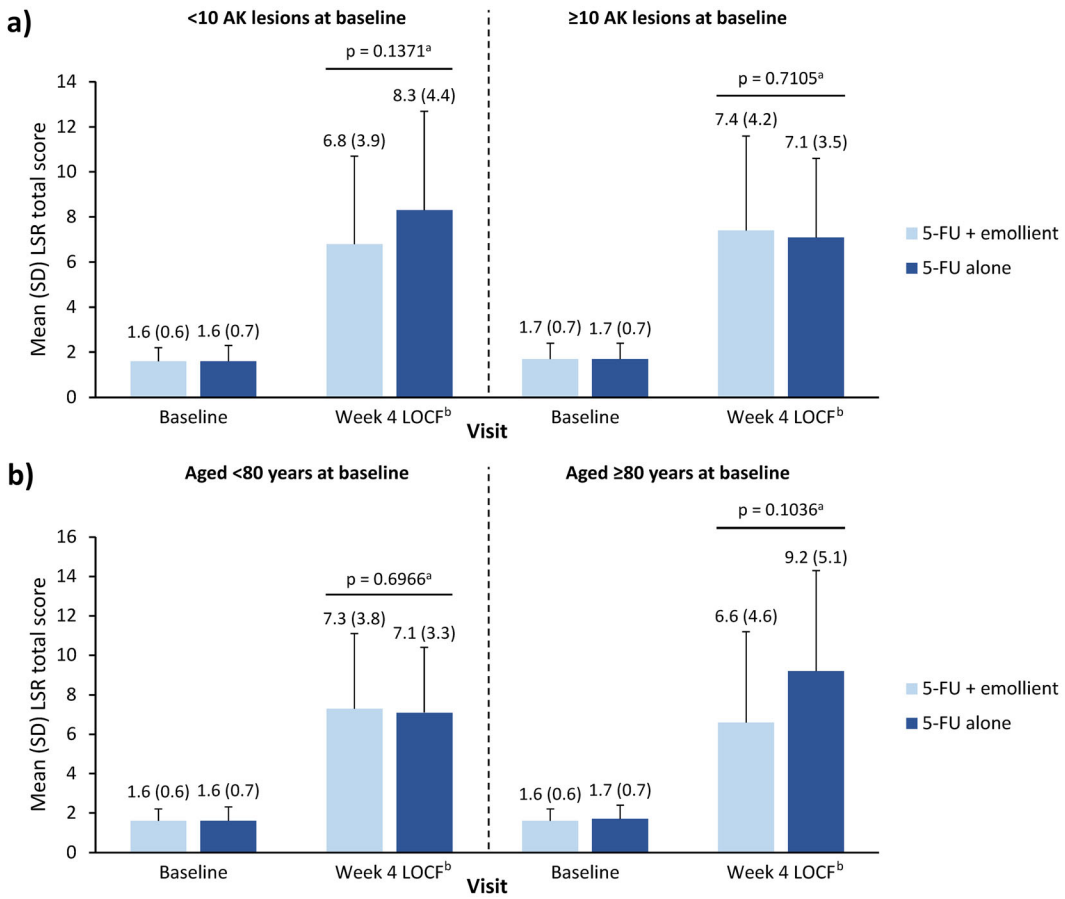


Fig. 3 Local skin reaction total scores at baseline and week 4 with 4% 5-FU plus emollient or 4% 5-FU alone in subgroups defined by (**a**) number of AK lesions at baseline and (**b**) age at baseline (full analysis set). *5-FU* 5-fluorouracil, *AK* actinic keratosis, *LOCF* last observation carried forward, *LSR* local skin reaction, *SD* standard deviation. **a** Two-sided test for treatment effect. **b** LSR score at week 4, or at an optional visit or week 2 in cases of major local reaction

CI −1.49, +2.17; $p = 0.7105$; Fig. 3A). When assessed by patient age at baseline, the mean LSR total scores at week 4 also tended to favour the intervention group over the control group in patients aged ≥ 80 years (LSM difference −2.47; 95% CI −5.47, +0.53; $p = 0.1036$) but not in those aged < 80 years (LSM difference +0.28; 95% CI −1.14, +1.70; $p = 0.6966$; Fig. 3B), although the between-group difference was not statistically significant in either age category.

LSR total scores were similar at week 2 in the intervention group and control group (Fig. 2); at week 8 (i.e. 4 weeks after completion of 4% 5-FU treatment), LSR total scores had decreased in both treatment groups.

With regard to LSR scores for individual items, some patients presented with mild erythema (mean score of 0.8 in both groups), flaking/scaling (mean scores of 0.6 in the intervention group and 0.7 in the control group) and crusting (mean scores of 0.1 and 0.2, respectively) at baseline (Table 2). At weeks 2 and 4, the only item with a mean LSR score of > 2 was erythema in both the treatment groups, and by week 8, all items had mean LSR scores of < 1 (Table 2). There were no statistically significant differences between treatment groups in the distribution of LSR scores (0 to 4)

for the individual items (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation and erosion/ulceration) at any time point (Fig. 4).

At week 4, the proportion of patients with a severe reaction (i.e. LSR score of 3 or 4) was non-significantly lower in the intervention group than in the control group for flaking/scaling (10.2% versus 17.2%) and crusting (15.3% versus 22.4%), while the proportion of patients with severe erythema, swelling, vesiculation/pustulation or erosion/ulceration reactions was similar in the two treatment groups (Table 3). The most frequent severe reaction at week 4 was erythema, occurring in 26 patients (44.1%) in the intervention group and 28 patients (48.3%) in the control group. LSRs were resolved by week 8 in most patients.

AK Lesion Clearance

The AK lesion clearance rates at week 8 were not significantly different between the treatment groups, with cCR rates of 38.6% in the intervention group and 33.3% in the control group ($p = 0.5200$), and pCR rates of 60.0% and 55.1%, respectively ($p = 0.5567$). The mean relative reduction in the number of AK lesions at week 8 was −72% in both groups ($p = 0.4585$).

Fig. 4 Proportion of patients in the 4% 5-FU plus emollient (intervention) group and 4% 5-FU alone (control) group with each individual local skin reaction item scores at baseline and weeks 2, 4 and 8 for (**a**) erythema, (**b**) flaking/scaling, (**c**) crusting, (**d**) swelling, (**e**) vesiculation/pustulation and (**f**) erosion/ulceration (full analysis set). *5-FU* 5-fluorouracil, *LSR* local skin reaction, *NE* not evaluable. **a** Calculated using the Cochran–Mantel–Haenszel test. No statistically significant between-group differences were observed for the distribution of scores (0–4) for the individual LSRs at any time point

Safety

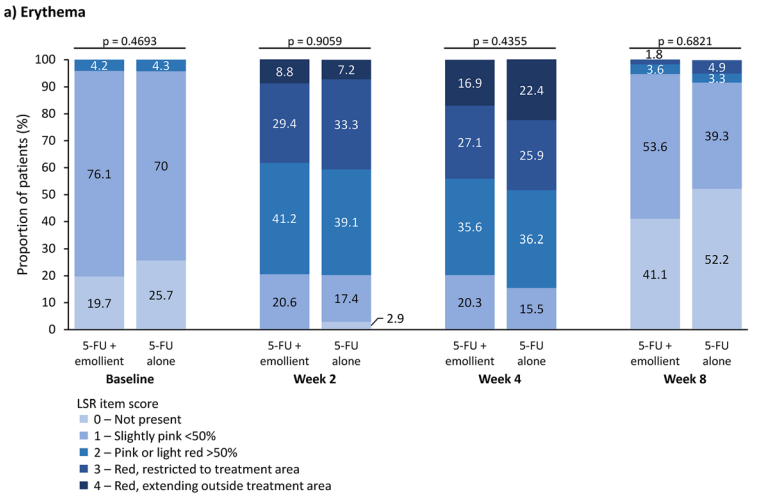
TEAEs occurred in 21 patients (28.8%) in the intervention group and 18 patients (25.4%) in the control group (Table 4). Skin reactions were the most common TEAEs in both the intervention and control groups, occurring in 13 patients in each group (17.8% and 18.3%, respectively), and leading to treatment discontinuation in 9 (12.3%) and 7 (9.9%) patients, respectively. TEAEs were considered study drug related in 15 (20.5%) and 13 (18.3%) patients, respectively.

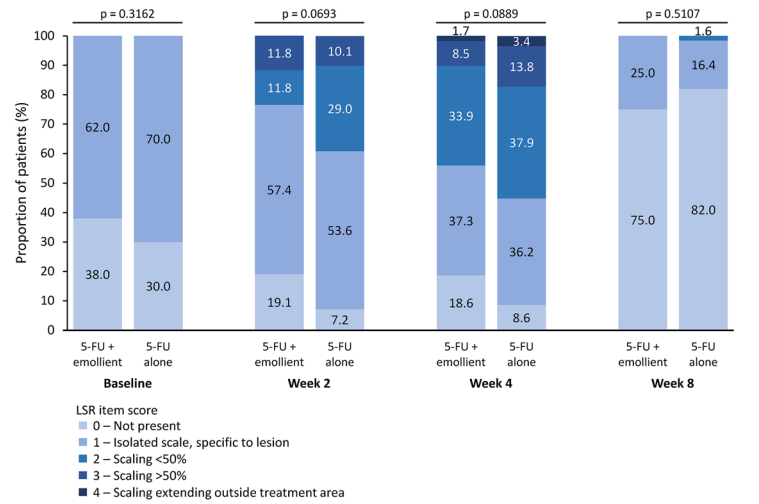
A serious AE leading to death occurred in only one patient; this patient (in the intervention group) had a myocardial infarction that was not considered to be related to the study drug. The patient had a history of cardiac disorders and was undergoing treatment for

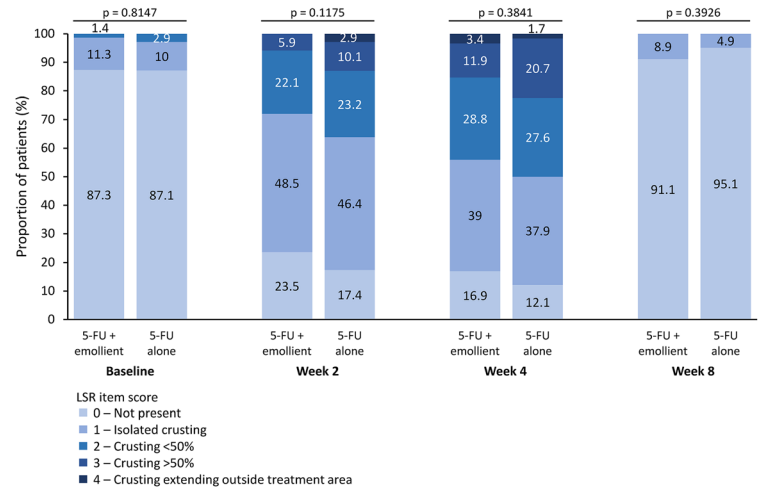
Table 2 Local skin reaction scores for individual items at each visit in patients with actinic keratosis (full analysis set)

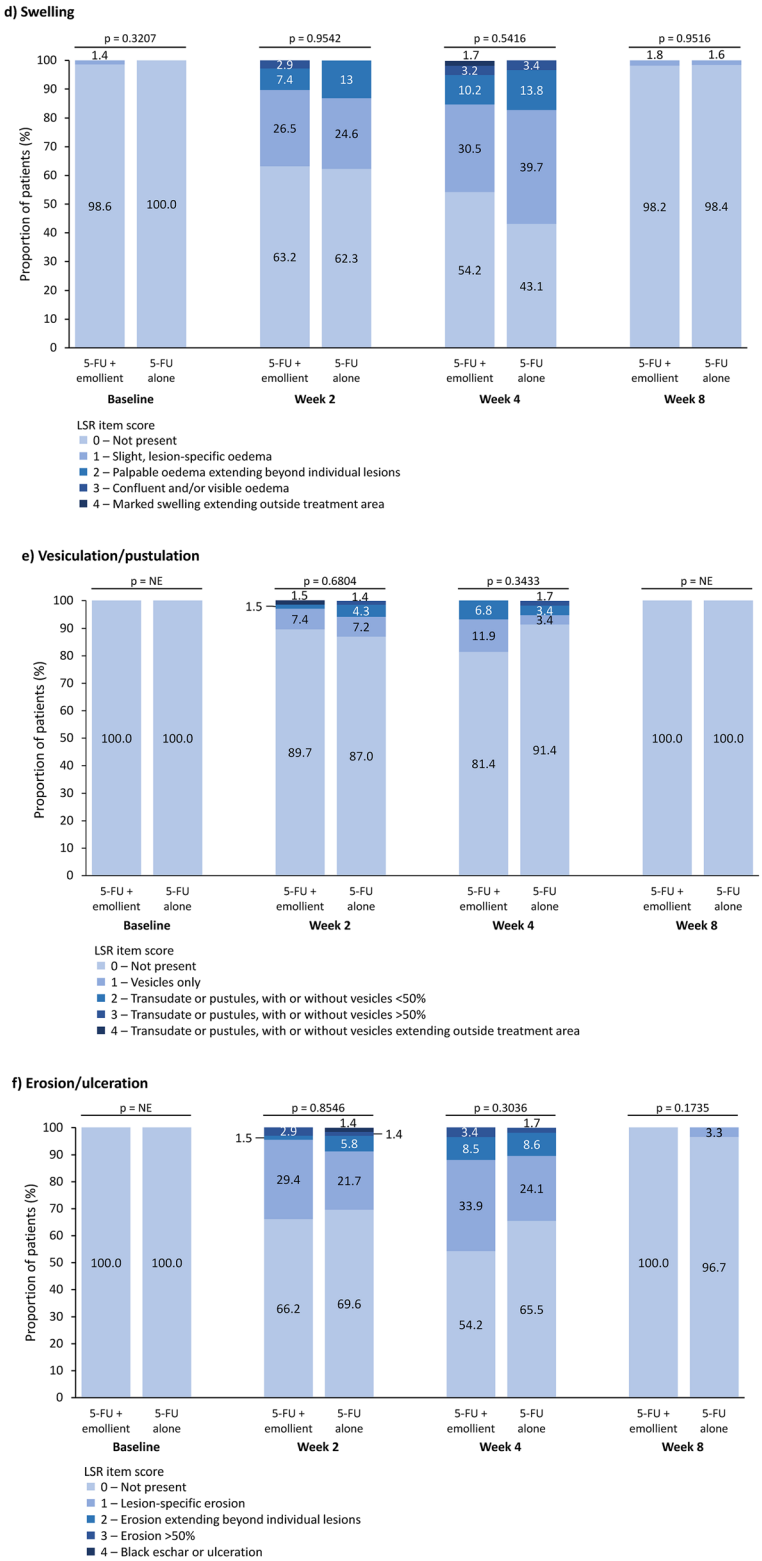
	4% 5-FU plus emollient ***n*** **= 71**				**4% 5-FU alone** ***n*** **= 70**			
	Baseline	**Week 2**	**Week 4**	**Week 8**	**Baseline**	**Week 2**	**Week 4**	**Week 8**
Individual LSR score, mean (SD)								
Erythema	0.8 (0.5)	2.3 (0.9)	2.4 (1.0)	0.7 (0.6)	0.8 (0.5)	2.2 (0.9)	2.6 (1.0)	0.6 (0.8)
Flaking/scaling	0.6 (0.5)	1.2 (0.9)	1.4 (0.9)	0.3 (0.4)	0.7 (0.5)	1.4 (0.8)	1.7 (0.9)	0.2 (0.4)
Crusting	0.1 (0.4)	1.1 (0.8)	1.5 (1.0)	0.1 (0.3)	0.2 (0.4)	1.3 (1.0)	1.6 (1.0)	0 (0.2)
Swelling	0 (0.1)	0.5 (0.8)	0.7 (0.9)	0 (0.1)	0	0.5 (0.7)	0.8 (0.8)	0 (0.1)
Vesiculation/postulation	0	0.2 (0.6)	0.3 (0.6)	0	0	0.2 (0.6)	0.2 (0.6)	0
Erosion/ulceration	0	0.4 (0.7)	0.6 (0.8)	0	0	0.4 (0.8)	0.5 (0.7)	0 (0.2)

5-FU 5-fluorouracil, *LSR* local skin reaction, *SD* standard deviation


a) Erythema
p = 0.4693
p = 0.9059
p = 0.4355
p = 0.6821
Proportion of patients (%)
4.2
4.3
76.1
70
19.7
25.7
8.8
7.2
29.4
33.3
41.2
39.1
20.6
17.4
2.9
16.9
22.4
27.1
25.9
35.6
36.2
20.3
15.5
1.8
3.6
4.9
3.3
53.6
39.3
41.1
52.2
5-FU + emollient
5-FU alone
Baseline
Week 2
Week 4
Week 8
LSR item score
0 – Not present
1 – Slightly pink <50%
2 – Pink or light red >50%
3 – Red, restricted to treatment area
4 – Red, extending outside treatment area


b) Flaking/scaling
p = 0.3162
p = 0.0693
p = 0.0889
p = 0.5107
Proportion of patients (%)
62.0
70.0
38.0
30.0
11.8
10.1
11.8
29.0
57.4
53.6
19.1
7.2
1.7
8.5
3.4
13.8
33.9
37.9
37.3
36.2
18.6
8.6
25.0
1.6
16.4
75.0
82.0
5-FU + emollient
5-FU alone
Baseline
Week 2
Week 4
Week 8
LSR item score
0 – Not present
1 – Isolated scale, specific to lesion
2 – Scaling <50%
3 – Scaling >50%
4 – Scaling extending outside treatment area


c) Crusting
p = 0.8147
p = 0.1175
p = 0.3841
p = 0.3926
Proportion of patients (%)
1.4
2.9
11.3
10
87.3
87.1
5.9
2.9
22.1
10.1
48.5
23.2
46.4
23.5
17.4
3.4
1.7
11.9
20.7
28.8
27.6
39
37.9
16.9
12.1
8.9
4.9
91.1
95.1
5-FU + emollient
5-FU alone
Baseline
Week 2
Week 4
Week 8
LSR item score
0 – Not present
1 – Isolated crusting
2 – Crusting <50%
3 – Crusting >50%
4 – Crusting extending outside treatment area



◀**Fig. 4** continued

multiple comorbidities, including hypertension, hypercholesterolaemia, diabetes mellitus and heart valve incompetence.

DISCUSSION

This phase IV clinical trial in adults with AK lesions showed that the local tolerability and effectiveness of 4% 5-FU were similar with and without the addition of an emollient. The study did not meet its primary objective, as the mean LSR total scores at week 4 showed no statistically significant differences between patients who received 4% 5-FU plus emollient and patients who received 4% 5-FU alone. The proportion of patients with a severe LSR at week 4 was non-significantly lower in the intervention

Table 3 Severe and non-severe local skin reactions at week 4 (full analysis set)

LSR item, *n* (%)	4% 5-FU plus emollient *n* = 59[a]		4% 5-FU alone *n* = 58[a]	
	Non-severe[b]	Severe[c]	Non-severe[b]	Severe[c]
Erythema	33 (55.9)	26 (44.1)	30 (51.7)	28 (48.3)
Flaking/scaling	53 (89.8)	6 (10.2)	48 (82.8)	10 (17.2)
Crusting	50 (84.7)	9 (15.3)	45 (77.6)	13 (22.4)
Swelling	56 (94.9)	3 (5.1)	56 (96.6)	2 (3.4)
Vesiculation/pustulation	59 (100.0)	0	57 (98.3)	1 (1.7)
Erosion/ulceration	57 (96.6)	2 (3.4)	57 (98.3)	1 (1.7)

5-FU 5-fluorouracil, *LSR* local skin reaction
[a]Data missing for 12 patients in each treatment group
[b]Defined as an LSR item score of 0, 1 or 2
[c]Defined as an LSR item score of 3 or 4

Table 4 Summary of all treatment-emergent adverse events

	4% 5-FU plus emollient *n* = 73		4% 5-FU alone *n* = 71	
	n (%)	Number of events[a]	*n* (%)	Number of events[a]
Patients with at least one TEAE	21 (28.8)	23	18 (25.4)	29
Patients with at least one treatment-related TEAE[b]	15 (20.5)	16	13 (18.3)	17
Patients with at least one AE leading to definitive study drug discontinuation	12 (16.4)	12	8 (11.3)	9
Patients with at least one serious AE	1 (1.4)	1	0	0

5-FU 5-fluorouracil, *AE* adverse event, *TEAE* treatment-emergent adverse event
[a]The occurrence of an AE was defined by the appearance of a new single event, the reappearance of a previously recovered event, or the worsening of a continuous event (relative to its previous status)
[b]AE with a relationship to the study drug other than 'not suspected'

versus the control group for flaking/scaling (10.2% versus 17.2%) and crusting (15.3% versus 22.4%), while there were no between-group differences for the incidence of severe erythema, swelling, vesiculation/pustulation and erosion/ulceration reactions. Although the addition of an emollient did not significantly reduce LSR severity compared with 5-FU alone, the LSR total score in the intervention arm (mean score of 7.1) was at the expected level to show a difference with the control arm (i.e. 7.0), while the LSR total score in the control arm (mean score of 7.7) was better than the expected score (i.e. 10). The latter score was estimated using raw data of the signs of local tolerance from a previous clinical trial of topical 4% 5-FU [23]. Of note, skin reactions led to treatment discontinuation in only 9.9% of patients in the control arm.

The 4% 5-FU formulation contains highly purified peanut oil, which has effective moisturising properties and is safe for use even in patients with peanut allergy [23]. This moisturising property of peanut oil in this 4% 5-FU formulation could be one of the reasons why our study observed no differences in the individual LSR items (i.e. erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation and erosion/ulceration) between the intervention and control groups. However, a trend was observed for crusting and flashing/scaling, indicating that the addition of a second emollient could provide additional benefit for these symptoms.

The severity of LSRs has previously been related to the number of AK lesions at baseline (described below) [21]; therefore, the lower than expected LSR total score in the control arm of this study may be explained by the lower mean number of AK lesions at baseline (12.2 lesions per patient) compared with the previous clinical trials of topical 5-FU (15 lesions per patient) [23].

When LSR total scores at week 4 were compared in the subgroup analysis according to the number of lesions at baseline (< 10 and ≥ 10) or age (< 80 and ≥ 80 years), no statistically significant differences were observed between the intervention and control groups. However, in patients with < 10 lesions at baseline, the LSM between-group difference of -1.51 (95% CI -3.51, $+0.49$) indicated a possibly clinically relevant effect of the emollient in these patients with less damaged skin. Similarly, patients aged ≥ 80 years had an LSM between-group difference of -2.47 (95% CI -5.47, $+0.53$), which suggests a clinically relevant favourable effect of the emollient in older patients, who often have very dry skin [25]. Further studies in larger patient populations are needed to verify the potential clinical benefits of adding emollient to 4% 5-FU in older patients or in those with < 10 AK lesions at treatment initiation.

As expected, skin reactions were the most common TEAEs in both the groups; however, there were no new safety signals with the addition of an emollient to the 4% 5-FU treatment regimen.

The rates of complete and partial AK lesion clearance were similar between the treatment groups, confirming that the additional use of an emollient did not compromise the effectiveness of topical 4% 5-FU cream. At week 8, the mean relative reduction in total number of AK lesions versus baseline was -72% in both groups, which is in line with the findings of previous clinical studies of 4% 5-FU (-80%) [23].

The limitations of our study include its single-blind study design, although given the nature of the treatments and their application, a double-blind study design was not feasible. However, all efforts were made to maintain the investigator blinding throughout the study.

CONCLUSIONS

The local tolerability of 4% 5-FU remained at an acceptable level, with better LSR total scores than expected. The safety and effectiveness of 4% 5-FU topical cream for the treatment of adults with AK lesions were not significantly modified by the addition of an emollient to the treatment regimen. The emollient may be beneficial in patients with < 10 lesions at baseline or in older patients and may provide slight reductions in severe flaking/scaling and crusting LSRs.

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