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A randomized trial comparing simultaneous vs. sequential field treatment of actinic keratosis with ingenol mebutate on two separate areas of the head and body

G. Pellacani,1,* K. Peris,2 C. Guillen,3 F. Clonier,4 T. Larsson,4 R. Venkata,4 S. Puig5
1Department of Dermatology, University of Modena and Reggio Emilia, Modena, Italy
2Department of Dermatology, Catholic University of Rome, Rome, Italy
3Department of Dermatology, Instituto Valenciano de Oncología, Valencia, Spain
4LEO Pharma A/S, Ballerup, Denmark
5Melanoma Unit, Dermatology Department, Hospital Clinic of Barcelona, University of Barcelona & CIBERER, Instituto de Stud Carlos III, Barcelona, Spain
*Correspondence: G. Pellacani. E-mail: Pellacani.giovanni@unimore.it

Abstract
Background Actinic keratoses (AKs) are precursors to invasive squamous cell carcinoma and can progress if untreated. Limited data support the use of ingenol mebutate to treat AKs on more than one area of the body simultaneously.
Objective To investigate safety, efficacy and treatment satisfaction when treating separate areas simultaneously or sequentially with different concentrations of ingenol mebutate gel.
Methods In this phase IIIb study (NCT01787383), patients with clinically visible, non-hyperkeratotic AKs on two separate treatment areas (face/scalp and trunk/extremities) were randomized to simultaneous or sequential treatment with ingenol mebutate gel (0.015% and 0.05%). Endpoints included composite local skin response (LSR) score 3 days after first application, complete AK clearance and percentage reduction in AKs at week 8.
Results There were no statistically significant differences between simultaneous (n = 101) and sequential (n = 98) groups in composite LSR score (10.4 vs. 9.7), complete clearance (52.7% vs. 46.9%) or percentage reduction in AKs (83.4% vs. 79.1%). Mean composite LSR scores on face/scalp and trunk/extremities were similar for both groups. Adverse event (AE) incidence was comparable between groups, the most common treatment-related AEs being pruritus and pain at the application site.
Conclusion Treating AKs with ingenol mebutate simultaneously or sequentially gave similar results in terms of tolerability (LSR score, AEs) and efficacy (complete clearance). Therefore, the physician and patient can select the most convenient treatment regimen, with confidence in achieving a similar outcome.
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Conflicts of interest
GP has received consultancy fees from LEO Pharma. KP has received advisory/speaker honoraria from LEO Pharma, MEDA, Novartis and Roche. CG has received grants/consultancy fees or speaker honoraria from LEO Pharma, Galderma, Almirall, Meda and ISDIN. SP has received advisory/speaker honoraria or grants from LEO Pharma, Roche, ISDIN and Almirall. FC, TL and RV are employees of LEO Pharma.

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Introduction
Actinically damaged skin is at increased risk of emergent malignancy, an effect known as field cancerization,1–4 which is characterized by the presence of multiple subclinical and clinically visible lesions.5,6 Actinic keratoses (AKs) are epidemiologically linked to and may be considered precursors of invasive squamous cell carcinoma (SCC),7–10 with indications that 60–65% of SCCs may emerge from the site of an AK lesion.7 As the risk of an individual AK progressing to invasive SCC cannot be predicted,11 treating the entire field is favoured over lesion-directed therapy.12
Field therapy has been shown to prevent the progression of subclinical lesions in the long term, giving rise to low recurrence rates compared with lesion-directed therapy.\textsuperscript{13,14} Studies and clinical practice have shown that the presence of multiple AKs indicates a greater risk of developing invasive non-melanoma skin cancer and that early treatment of AKs reduces the probability of progression.\textsuperscript{10,15} Additionally, certain risk factors including older age, fair skin and baldness are associated with a greater degree of actinic damage.\textsuperscript{1,16} Population-based studies investigating AK prevalence and its associated risk factors concluded that elderly patients with European ancestry and high cumulative sun exposure have the highest risk of developing AKs.\textsuperscript{17–21} Previous history of skin cancer is another risk factor, as shown by the baseline characteristics of previous AK study populations.\textsuperscript{22}

Ingenol mebutate gel was developed for the treatment of AK. It eradicates AKs by a dual mechanism that includes direct induction of cell death in proliferating keratinocytes, and stimulation of an inflammatory response.\textsuperscript{13} Phase III clinical studies have shown ingenol mebutate to be an effective and well-tolerated field therapy for AK lesions on the head and body on areas up to 25 cm\textsuperscript{2}.\textsuperscript{22,23} The safety of ingenol mebutate has also been demonstrated on areas up to 100 cm\textsuperscript{2}.\textsuperscript{24} This study aimed to broaden the clinical utility of ingenol mebutate by evaluating the safety and efficacy of ingenol mebutate gel when applied either simultaneously or sequentially to AKs in two separate locations on the head and body.

**Methods**

**Study design and patient population**

This was a phase IIIb, multicentre, randomized, two-arm, parallel-group, open-label, 16-week trial conducted at 24 sites in Italy and Spain (NCT01787383). The protocol was approved by the relevant independent ethics committees and institutional review boards and the clinical trial conformed to the principles of the Declaration of Helsinki. Informed written consent was obtained from all patients.

Patients 18 years and older with four to eight clinically typical, visible, discrete, non-hyperkeratotic AK lesions on two separate 25 cm\textsuperscript{2} treatment areas on the face/scalp, and on the trunk/extremities, were enrolled into the study. Patients were excluded if the selected treatment areas were on periorbital skin, within 5 cm of an incompletely healed wound, or within 10 cm of a basal cell carcinoma or SCC. Other exclusion criteria included: prior treatment with ingenol mebutate; hypertrophic or hyperkeratotic lesions in the treatment area; non-responsive lesions (i.e. did not respond to cryotherapy on two occasions); and history of skin conditions other than AK (such as eczema, unstable psoriasis or xeroderma pigmentosum), which might interfere with the study evaluations.

The primary objective of the trial was to compare the safety of ingenol mebutate gel (0.015% and 0.05%) when applied either simultaneously or sequentially in two areas with AK lesions on the head (face/scalp) and the body (trunk/extremities). The secondary objectives were to determine efficacy and treatment satisfaction.

**Study treatment**

Eligible patients were randomized 1 : 1 to either simultaneous or sequential treatment with ingenol mebutate gel. Randomization was stratified by country and by anatomical location for face/scalp and trunk/extremities through an interactive voice/web response system. In the sequential group, the order of treatment areas (face/scalp first or trunk/extremities first) had equal weighting.

Ingenol mebutate 0.015% gel was self-applied to the face/scalp once daily for 3 days and ingenol mebutate 0.05% gel to the trunk/extremities for 2 days. Patients in the simultaneous group were treated with ingenol mebutate gel in both areas from day 1 (Visit 1). Patients in the sequential group treated one area with ingenol mebutate gel from day 1 (Visit 1) and then treated the second area 8 weeks later. The treatment schedule and investigator/patient assessments included identification of the selected treatment areas; AK lesion counts; local skin responses (LSRs); adverse events (AEs) and patient assessment (including Treatment Satisfaction Questionnaire for Medication [TSQM]\textsuperscript{25}) (Fig. 1).

The first single dose of ingenol mebutate gel was applied to each treatment area (simultaneous treatment) or the first treatment area (sequential treatment) under the direct supervision and management of study site staff on the first treatment day, according to the randomization schedule. The patient performed subsequent application(s) of ingenol mebutate gel at home, having been instructed how to spread the contents of the single dose tube evenly over the selected treatment area. Patients in the sequential arm received their second treatment cycle at week 8 and performed the subsequent applications of ingenol mebutate gel at home.

The primary endpoint was composite LSR score 3 days after the first ingenol mebutate application to each treatment area. The secondary endpoints included complete clearance of AK lesions, percentage reduction in AK lesions in the treatment areas and the TSQM 8 weeks after treatment. TSQM mainly evaluates three elements of treatment satisfaction, with patient evaluation of effectiveness, side-effects, convenience and global satisfaction.\textsuperscript{25}

**Statistical methods**

A sample size of 94 patients per group was required to obtain a 90% power to detect a difference of two points in composite LSR score assuming a standard deviation of 4.2. One hundred patients were to be enrolled for each of the two regimens, allowing for a discontinuation rate of 5%. Analysis of composite LSR score and AEs was carried out on the safety analysis set (all patients who received at least one application of trial medication).
For the primary endpoint analysis, LSRs were assessed at each visit using a standardized scale,26 with a composite score calculated from the sum of individual LSR scores (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation and erosion/ulceration; maximum composite score of 24). Composite LSR score for the simultaneous and sequential groups was analysed 3 days after starting the treatment for each area using a Wilcoxon signed rank test and an analysis of variance (ANOVA) with factors of treatment group, anatomical location and country and with a random subject effect. Efficacy analyses were based on the full analysis set, which was defined as all randomized patients. Missing values were not imputed. Complete clearance of AK lesions 8 weeks after treatment of each separate area was analysed by logistic regression, with factors of treatment group, anatomical location and country and with a random subject effect. Efficacy analyses were based on the full analysis set, which was defined as all randomized patients. Missing values were not imputed. Complete clearance of AK lesions 8 weeks after treatment of each separate area was analysed by logistic regression, with factors of treatment group, anatomical location and country and with a random subject effect. Percentage reduction in the number of AKs 8 weeks after treatment of each separate area was analysed similar to the LSR score; TSQM was analysed using a Wilcoxon signed rank test and an ANOVA with factors of treatment group, stratification group (face, scalp) and country.

Results

Study population
Between March 2013 and October 2013, 199 patients were enrolled and randomized in the trial, 101 patients to the simultaneous group and 98 to the sequential group (Fig. 2). Demographics and AK characteristics are shown in Table 1. The mean age was 74.5 years. Most patients had been treated previously for AK with cryosurgery on the face (simultaneous 55.1%, sequential 43.6%). All patients had AKs on the trunk and extremities, with most lesions on the back of the hand (simultaneous 44.6% and sequential 37.9%). In the simultaneous group, 94.1% of patients received the full dose for both areas (81.6% in the sequential group). Nine patients from the simultaneous group discontinued the study, including seven defined as ‘other’ reasons: four for wrong treatment area size and three for using the wrong treatment kit. Twenty-two patients from the sequential group discontinued the study, mostly for voluntary or other reasons, including one for wrong treatment area size, five for using the wrong treatment kit and two for fear of LSRs. Seventeen patients withdrew from the study before the second treatment cycle. Two patients from the simultaneous group and one from the sequential group withdrew because of unacceptable AEs, one of which was treatment-related (Fig. 2). Slightly higher levels of adherence were seen in the simultaneous treatment group than in the sequential treatment group, with 94.1% vs. 87.8% for face/scalp and 97.0% vs. 92.9% for trunk/extremities, respectively.

Safety
The mean composite LSR scores 3 days after treatment initiation for the simultaneous group and the sequential group showed no
A total of 32 AEs were reported by 22 patients (21.8%) in the simultaneous treatment group compared with the sequential group, no AE was reported for >1% of the patients. Two patients from the simultaneous group withdrew following AEs of SCC of the skin and scotoma, and one patient from the sequential group due to haemorrhagic erosive gastritis. The case of SCC of the skin was assessed as being treatment-related by the investigator, and the scotoma was not assessable, whilst the case of haemorrhagic erosive gastritis was considered to be unrelated to treatment. The SCC of the skin and haemorrhagic erosive gastritis were later classed as serious AEs by the investigator.

### Table 1 Patient demographics and AK characteristics

|                      | Full analysis set (n = 199) | Simultaneous group (n = 101) | Sequential group (n = 98) |
|----------------------|----------------------------|----------------------------|--------------------------|
| **Sex, n (%)**       |                            |                            |                          |
| Male                 | 168 (84.4)                 | 88 (87.1)                  | 80 (81.6)                |
| Female               | 31 (15.6)                  | 13 (12.9)                  | 18 (18.4)                |
| **Race, n (%)**      |                            |                            |                          |
| White                | 198 (99.5)                 | 100 (99.0)                 | 98 (100.0)               |
| **Skin type, n (%)** |                            |                            |                          |
| I – Burns easily,    |                            |                            |                          |
| never tans           | 25 (12.6)                  | 13 (12.9)                  | 12 (12.2)                |
| II – Burns easily,   |                            |                            |                          |
| tans minimally       | 136 (68.3)                 | 69 (68.3)                  | 67 (68.4)                |
| III – Burns moderately, tans gradually (light brown) | 38 (19.1) | 19 (18.8) | 19 (19.4) |
| **Age (years), mean**| 74.5                       | 74.4                       | 74.5                     |
| **Duration of AK**   |                            |                            |                          |
| (years), median (range) | 6.0 (0–33)              | 6.0 (0–31)                 | 6.0 (0–33)               |
| **Baseline AK lesion count, median (range)** | 5.0 (4–8) | 6.0 (4–12) |
| **Patients previously treated for AK, n (%)** | 87 (46.1) | 83 (44.7) |
| **AK treatment history, n (%)** |                          |                            |                          |
| Cryotherapy/liquid nitrogen | 44 (34.6) | 54 (55.1) |
| Surgical excision/curettage | 24 (23.8) | 17 (17.3) |
| Dermabrasion         | 3 (3.0)                    | 3 (3.1)                    |                          |
| Chemical peel*       | 0 (0.0)                    | 1 (1.0)                    |                          |
| Laser resurfacing    | 1 (1.0)                    | 0 (0.0)                    |                          |
| 5-fluorouracil       | 6 (5.9)                    | 3 (3.1)                    |                          |
| Imiquimod            | 22 (21.8)                  | 24 (24.5)                  |                          |
| Diclofenac           | 38 (37.6)                  | 25 (25.5)                  |                          |
| Photodynamic therapy | 42 (41.6)                  | 34 (34.7)                  |                          |
| Retinoids            | 0 (0.0)                    | 6 (6.1)                    |                          |
| Other                | 8 (7.9)                    | 9 (9.2)                    |                          |

*At least medium depth chemical peel. AK, actinic keratosis.

with no statistically significant difference between the two treatment groups (P = 0.34). Complete clearance rates were similar for face/scalp in the simultaneous and sequential treatment groups (53.3% vs. 50.0% respectively), although for trunk/extremities, the simultaneous treatment group had numerically higher clearance rates than the sequential group (52.2% vs. 43.6%). The mean percentage reduction in number of AKs was similar in the simultaneous and sequential groups (83.4% and 79.1% respectively; P = 0.20).

### Patient-reported outcomes

Patient treatment satisfaction was measured using TSQM scores on a scale of 0–100, where higher scores equate to better outcomes. The simultaneous and sequential groups did not differ statistically significantly different (10.4 vs. 9.7, respectively; P = 0.13). Mean composite LSR scores were similar in the simultaneous and sequential treatment groups for face/scalp (11.8 and 10.6 respectively) and trunk/extremities (9.1 and 8.8 respectively). LSR profiles between treatment groups were comparable, peaking at day 3 and returning to baseline levels within 30 days (Fig. 3a,b). Higher scores were observed for the face, scalp and chest in both treatment groups (Fig. 4).

A total of 32 AEs were reported by 22 patients (21.8%) in the simultaneous treatment group compared with the sequential treatment group where 25 AEs were reported by 22 patients (22.4%); see Table 2 for a summary of AEs. All AEs reported within the treatment areas were considered to be related to study drug by the investigator, and were more frequently experienced by patients in the simultaneous group than those in the sequential group (Table 2). Application-site pruritus and pain were the most common AEs observed within the treatment area of patients in the simultaneous group (eight patients and five patients respectively), and in the sequential group, no AE was reported for >1% of the patients. Two patients from the simultaneous group withdrew following AEs of SCC of the skin and scotoma, and one patient from the sequential group due to haemorrhagic erosive gastritis. The case of SCC of the skin was classed as being treatment-related by the investigator, and the scotoma was not assessable, whilst the case of haemorrhagic erosive gastritis was considered to be unrelated to treatment. The SCC of the skin and haemorrhagic erosive gastritis were later classed as serious AEs by the investigator.

### Efficacy

Complete clearance rates for the simultaneous and sequential treatment groups were 52.7% and 46.9% respectively (Fig. 5)
significantly in terms of TSQM scores for treatment effectiveness (mean: 63.1 and 66.4, respectively; \( P = 0.38 \)), side-effects after the first 8 weeks of treatment (mean: 93.1 and 95.1, respectively; \( P = 0.36 \)), convenience (mean: 73.7 and 74.7 respectively; \( P = 0.66 \)) or global satisfaction (mean: 64.6 and 67.4 respectively; \( P = 0.37 \)).

**Discussion**

This phase IIIb study compared the safety and efficacy of ingenol mebutate gel (0.015% and 0.05%) when applied simultaneously or sequentially to AKs in two areas on the head and body. Treatment duration and LSR resolution times are short with ingenol mebutate in comparison with other field therapy treatments.14 In addition, the LSR profile in this study was consistent with results already observed in pivotal studies22 and was nearly identical between the two treatment groups. We found no difference between the number of AEs in the simultaneous and sequential treatment groups, and the number of AEs was low in both. The safety profile did not vary by treatment area and was consistent with other studies: in one 12-month follow-up study of 108 patients treated with ingenol mebutate, only three AEs were identified in treatment areas; none was considered related to ingenol mebutate and none was SCC.23 In another 12-month study in 329 patients, three cases of SCC of skin were observed in the vehicle control group and none in the ingenol mebutate group.13

The favourable rate of complete clearance in the simultaneous treatment group means that patients can receive their treatment for both areas in one visit, rather than having to return to the clinic for a second cycle of treatment. A possible limitation of this study is

**Table 2** Summary of adverse events over the study duration (safety analysis set)

| AEs                                      | Simultaneous (n = 101) | Sequential (n = 98) |
|------------------------------------------|------------------------|---------------------|
|                                          | Number of AEs          | Number of patients, n (%) | Number of AEs | Number of patients, n (%) |
| All AEs                                  | 32                     | 22 (21.8)           | 25            | 22 (22.4)           |
| Severe AEs                               | 2                      | 2 (2.0)             | 2             | 2 (2.0)             |
| Treatment-related AEs                    | 23                     | 19 (18.8)           | 7             | 7 (7.1)             |
| AEs within treated areas                 | 16                     | 15 (14.9)           | 4             | 4 (4.1)             |
| AEs leading to withdrawal from trial     | 2                      | 2 (2.0)             | 1             | 1 (1.0)             |
| Serious AEs                              | 3                      | 3 (3.0)             | 4             | 4 (4.1)             |

AE, adverse event.
that fewer patients returned for a second cycle of treatment in the sequential arm, but this discontinuation rate was not for treatment-related reasons, but was defined as voluntary or other reasons, suggesting that a sequential dosing schedule requiring follow-up visits was less convenient in this patient population. Although details of the reasons for discontinuation defined as ‘other’ and ‘voluntary’ are difficult to specify, only two patients indicated fear of LSRs, suggesting that this was not a major contributor to dropping out. Five patients are difficult to specify, only two patients indicated fear of LSRs, suggesting that this was not a major contributor to dropping out. Five patients in the sequential group, and three in the simultaneous treatment group, had used the wrong treatment kit (defined as other reason) and were thus discontinued. A second cycle of treatment was well tolerated, with high TSQM scores and high treatment adherence. In fact, in the TSQM analysis, the score for convenience did not differ significantly between the two groups, suggesting that LSRs did not impact on patient self-evaluation of treatment at week 8.

Shergill et al. have shown that duration of treatment can be associated with increasing rates of non-adherence to topical therapy (adjusted odds ratio for treatment durations greater than 4 weeks = 2.2, \( P < 0.01 \)). Trials of ingenol mebutate have reported that the short duration of treatment supports very high (>98%) adherence compared with other topical AK treatments. The results from this study suggest that when selecting either a simultaneous or sequential treatment plan, there is a need to educate patients on what to expect from their treatment in terms of LSRs. In this trial, in the simultaneous arm, patients were able to administer the appropriate treatments by treatment area without confusion, supporting the fact that both dose formulations can be prescribed simultaneously with appropriate patient education.

The positive TSQM findings across the treatment groups suggest that a non-invasive, self-administered topical treatment may be preferred in patients with multiple or recurrent AK lesions. A simultaneous treatment schedule is likely to have benefits in both health resource allocation and patient convenience, as a patient would not need to return to the clinic for a second visit. In any case, topical field treatment is beneficial compared with lesion-directed treatment. In a clinical study where all visible baseline lesions were treated with cryosurgery followed by either ingenol mebutate gel or vehicle, ingenol mebutate showed long-term added benefits in the suppression of both baseline and emerging lesions, presumably through an effect on subclinical AK lesions.

In conclusion, both simultaneous and sequential treatment of AK with ingenol mebutate showed a similarly acceptable safety and tolerability profile, with a high efficacy in clearing multiple AK lesions on both head and body locations. Ultimately, the treatment schedule is based on agreement between the physician and the patient; this study helps to support the selection of the most appropriate regimen to treat AK in individual patients.

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References

1. Braakhuis BJ, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res 2003; 63: 1727–1730.
2. Jonason AS, Kunala S, Price GI et al. Frequent clones of p53-mutated keratinocytes in normal human skin. Proc Natl Acad Sci U S A 1996; 93: 14025–14029.
3. Vanharanta S, Massague J. Field cancerization: something new under the sun. Cell 2012; 149: 1179–1181.
4. Hu B, Castillo E, Harewood L et al. Multifocal epithelial tumours and field carcinogenesis from loss of mesenchymal CSE signaling. Cell 2012; 149: 1207–1220.
5. Lebwohl M. Actinic keratoses: epidemiology and progression to squamous cell carcinoma. Br J Dermatol 2003; 149(Suppl 66): 31–33.
6. Rosen T, Lebwohl MG. Prevalence and awareness of actinic keratoses: barriers and opportunities. J Am Acad Dermatol 2013; 68: S2–S9.
7. Criscione VD, Weinstein MA, Naylor MF, Luque C, Eide MJ, Bingham SF. Actinic keratoses: natural history and risk of malignant transformation in the Veterans Affairs Tropical Tretinoin Chemoprevention Trial. Cancer 2009; 115: 2523–2530.
8. Einspahr JG, Stratton SP, Bowden GT, Alberts DS. Chemoprevention of human skin cancer. Crit Rev Oncol Hematol 2002; 41: 269–285.
9. Vatve M, Ortonne JP, Birch-Machin MA, Gupta G. Management of field change in actinic keratosis. Br J Dermatol 2007; 157(Suppl 2): 21–24.
10. Werner RN, Sammain A, Erdmann R, Hartmann V, Stockfleth E, Nest A. The natural history of actinic keratoses: a systematic review. Br J Dermatol 2013; 169: 302–318.
11. Berman B, Cockerell CJ. Pathobiology of actinic keratoses: ultraviolet-dependent keratinocyte proliferation. J Am Acad Dermatol 2013; 68(Suppl 1): S10–S19.
12. Stockfleth E, Ferrandiz C, Grob JJ, Leigh I, Pehamberger H, Kerr H. Development of a treatment algorithm for actinic keratoses: a European Consensus. Eur J Dermatol 2008; 18: 651–659.
13. Berman B, Goldenberg G, Hanke CW et al. Efficacy and safety of ingenol mebutate 0.015% gel after cryosurgery of actinic keratosis: 12-month results. J Drugs Dermatol 2014; 13: 741–747.
14. Krawtchenko N, Roewert-Huber J, Ulrich M, Mann I, Sterry W, Stockfleth E. A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. Br J Dermatol 2007; 157(Suppl 2): 34–40.
15. Rigal DS, Stein Gold LF. The importance of early diagnosis and treatment of actinic keratoses. J Am Acad Dermatol 2013; 68(Suppl 1): S20–S27.
16. Flohil SC, van der Leest RJ, Dowlatshahi EA, Hofman A, De Vries E, Nijsten T. Prevalence of actinic keratoses and associated factors in a representative sample of the Italian adult population: results from the Prevalence of Actinic Keratoses Italian Study, 2003–2004. Arch Dermatol 2006; 142: 722–726.
22 Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. N Engl J Med 2012; 366: 1010–1019.
23 Lebwohl M, Shumack S, Gold LS, Melgaard A, Larsson T, Tyring SK. Long-term follow-up study of ingenol mebutate gel for the treatment of actinic keratoses. JAMA Dermatol 2013; 149: 666–670.
24 Anderson L, Jarrett M, Schmieder G, Schumack S, Katsamas J, Welburn P. Tolerability and pharmacokinetics of ingenol mebutate 0.05% gel applied to treatment areas up to 100 cm² on the forearm(s) of patients with actinic keratosis. J Clin Aesthet Dermatol 2014; 7: 19–29.
25 Atkinson MJ, Sinha A, Hass SL et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes 2004; 2: 12.
26 Rosen R, Marmur E, Anderson L, Welburn P, Katsamas J. A new, objective, quantitative scale for measuring local skin responses following topical actinic keratosis therapy. Dermatol Ther 2014; 4: 207–219.
27 Shergill B, Zokaie S, Carr AJ. Non-adherence to topical treatments for actinic keratosis. Patient Prefer Adherence 2013; 8: 35–41.