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Ingenol mebutate as topical treatment for actinic keratosis based on a prospective, non-interventional, multicentre study of real-life clinical practice in Germany: efficacy and quality of life

Background: The use of ingenol mebutate (IM) as a field-directed therapy over a short period of time has been shown to be effective and well tolerated in randomized Phase III trials. *Objectives:* To assess the efficacy and patient-reported outcomes for IM as treatment for actinic keratosis (AK) under daily "real-life" practice conditions. *Materials and Methods:* A total of 826 adult patients with AK were enrolled by 292 dermatologists in Germany in a prospective, open, non-interventional, non-controlled, multicentre study. All patients were treated with IM and followed for eight weeks. *Results:* The mean number of clinically visible AK lesions decreased significantly from 7.1±6.8 to 2.8±4.5 ($p<0.0001$). Most dermatologists (79.0%) rated global efficacy of IM as "very good"/"good" and 82.6% of the patients were "very satisfied" or "rather satisfied" with the efficacy of IM. Patient-reported outcomes showed greater efficacy and treatment comfort with IM compared to any last previous AK treatment with a comparable tolerability profile. Skin-related QoL data revealed a significant improvement of 50.2% after IM treatment ($p<0.0001$). Adverse events were reported in 7.0% of all patients, which were in most cases mild in intensity. *Conclusion:* Field-directed treatment with IM over a short period was associated with a high level of treatment satisfaction, as reported by dermatologists and patients. This observational study demonstrates the effectiveness and tolerability of IM in everyday clinical practice in addition to the known efficacy and safety obtained by randomized controlled clinical trials.

Key words: actinic keratosis, field-directed therapy, ingenol mebutate gel, quality of life, real-life clinical practice

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Actinic keratosis (AK) represents a common diagnosis in dermatological practice [1]. Although the actual risk of progression of single AK lesions to squamous cell carcinoma (SCC) remains unclear and no prognostic tools are available to predict the transformation of individual AK lesions to invasive SCC (iSCC), AK lesions are considered as "*in situ* SCC". Earlier studies have revealed a risk of progression to iSCC, of between 0.025% and 16% per year for any distinct AK lesion [2]. Thus, adequate treatment of AK lesions is presumed to be necessary [1, 3, 4].

Since AK lesions are typically surrounded by non-visible dysplastic keratinocytes (field cancerization), field-directed treatment strategies are indicated in order to eradicate atypical cells that may be clinically unsuspicious in the target area [5].

Field-directed treatments may be beneficial to lesion-directed therapies, such as cryotherapy or curettage, as they not only target clinically apparent AK lesions, but also address subclinical and emerging AK lesions [1, 4, 6]. Field-directed approaches include topical patient-administered medications, such as drugs with antimetabolite effects (topical 5-fluorouracil [5-FU]), topical non-steroidal anti-inflammatory drugs (diclofenac sodium, piroxicam) that inactivate COX isoforms and inhibit downstream prostaglandins, drugs with immunomodulatory properties (imiquimod and ingenol mebutate [IM]) or physician-administrated photodynamic therapy (PDT) [1, 4, 6-8].

IM gel is a field therapy indicated for the treatment of AK in adults for the face and scalp or trunk and extremities [9]. A dual mechanism of action has been proposed for IM: at high concentrations (> 100 μM) in the upper epidermis, IM causes rapid mitochondrial disruption leading to necrosis; at low concentrations (10-1000 nM) in the lower epidermis, IM stimulates a localized pro-inflammatory response via activation of the protein kinase C (PKC) pathway and apoptosis [10]. The induction of an inflammatory response may account for the occurrence of local skin responses (LSRs), such as erythema/flaking, and crusting after cutaneous application of IM [9]. In randomized, double-blind Phase III trials, IM applied topically for two to three days has been shown to be an effective and well-tolerated field treatment for AKs [11]. Patients had four to eight AK lesions within a contiguous 25-cm^2 treatment area on the face/scalp or

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trunk/extremities and achieved complete clearance of all AK lesions after eight weeks of follow-up in 42% and 34%, respectively. Lesion reduction was 83% for face/scalp and 75% for trunk/extremities. In the IM group, more than 98% of the patients adhered to the three-day dosing regimen [11]. However, data regarding real-life effectiveness, treatment comfort, and impact on quality of life (QoL) in routine clinical practice are still limited. In an observational study (n=88) evaluating the real-life effectiveness and adherence of IM, the lesion clearance rate of AKs was 82% on the face and 80% on the scalp with a treatment adherence rate of >99% [12]. The aspects of health care research, patient-reported outcome, and real-world evidence have become more important in recent years. This non-interventional study aimed to evaluate efficacy and tolerability as well as patient-reported outcomes, such as patient satisfaction, skin condition, and skin-related QoL before and after routine use with IM, in an outpatient setting.

Materials and methods

Study design

Adult patients of both genders eligible for treatment with IM were enrolled by 292 dermatologists in Germany in this prospective, open, non-interventional, non-controlled, multicentre study according to the following inclusion criterion: patients with non-hyperkeratotic, non-hypertrophic AK for whom the treating dermatologist had prescribed treatment with IM. Patients with any of the following exclusion criteria were excluded: previous use of IM; previous use of any other treatment for AK during the last eight weeks; presence of melanoma, non-melanoma skin cancers, and open wounds in the investigated treatment area(s); as well as contraindications according to the prescribing information. IM was prescribed for self-application by patients and used according to the prescribing information. Data were gathered at two visits: Visit 1 at the study start and Visit 2 at about eight weeks after initial treatment with IM (end of study). At Visit 1, the following data were reported by dermatologists: Fitzpatrick skin type, duration of AKs, number of AK lesions, presence of squamous cell and basal cell carcinoma (number of lesions and time of initial diagnosis), persistent skin anomalies on the target treatment field, last prior local treatment(s) of AK, usage of systemic immunosuppression, localization of skin area(s) treated with IM, and number of prescribed tubes.

For evaluation of treatment efficacy, the number of lesions was counted on the treated field(s) at both visits. At Visit 2, global efficacy and tolerability were assessed by dermatologists using a 5-point scale (unsatisfactory, sufficient, satisfactory, good, very good) as well as the occurrence of new skin anomalies in the treated field(s). Furthermore, the patients were asked whether they had performed the treatment as prescribed. At Visit 1, patients reported their sunlight exposure due to occupational and leisure activities (never, ≤1 years, >1 ≤10 years, >10 ≤20 years, >20 years). At Visit 1, treatment satisfaction regarding efficacy, tolerability, and treatment comfort with the last previous treatment was also assessed using a questionnaire including scales with the categories “not at all satisfied”, “a little satisfied”, “rather satisfied”, and “very satisfied”. At Visit 2, patients were asked to fill in the same questionnaire for the treatment with IM.

Data for patient-reported outcome for skin-related quality of life (QoL) within the last seven days were collected at Visit 1 and 2 using a validated German version [14] of the Skindex-16 questionnaire [13]. The average total score represents the sum of the scores for each question. In addition, patients answered questions regarding their skin condition (roughness, blotchiness, and wrinkling) based on a 4-point scale (0=none, 1=a little, 2=rather, 3=very).

Data management and statistical analysis

Data management was performed based on the Guidelines and Recommendations for Ensuring Good Epidemiological Practice (GEP) [15]. For quality assurance, data validation and plausibility checks were performed. As far as possible, inconsistent and/or implausible data were corrected. If this was not possible, a written query for clarification was sent to the dermatologist. Statistical evaluation was performed using the program system SAS^{TM} version 9.4. Changes in values were analysed using the Wilcoxon signed-rank test.

Results

Patient characteristics

In total, 826 patients with AK were included (*figure 1*). All patients were eligible for study participation according to inclusion and exclusion criteria. The mean duration of observation was 8.8±2.2 weeks. Of the patients, 70.7% were male (n=584) with a mean age of 73.2±9.7 years. About two thirds (66.2%) of patients had Fitzpatrick skin type II (n=545). The average time between initial AK diagnosis and the first assessment during the study (Visit 1) was 6.2±5.4 years. A total of 80.4% patients (664/826) had been previously treated for AK, mainly with topicals or cryotherapy (*table 1*). Among topical treatments, diclofenac sodium 3% gel (Solaraze®) was most commonly used (n=235), followed by imiquimod (Aldara®/Zyclara®; n=59), 5-FU (Efudix®/Actikerall®; n=50), and retinoids (n=4). A total of 334 patients (40.6%) had a previous history of non-melanoma skin cancer (basal cell carcinoma, n=205; squamous cell carcinoma, n=129) outside the AK target treatment area. Leisure time preferentially spent outdoors for more than 10 years of their lifetime was reported in 76.5% patients. Working predominantly outdoors for more than 10 years was reported by 28.2% patients. The presence of persistent skin anomalies within the selected target treatment field prior to the therapy with IM was reported in 26.5% patients (n=218). These were predominantly hyperpigmentation (n=152), hypopigmentation (n=112), skin atrophy (n=82), and scarring (n=53). At baseline, 16 patients (1.9%) reported previous immunosuppressive treatment, which was continued in 15 patients throughout this study.

Assessment by dermatologists

In total, 1,616 skin areas in 826 patients were treated with IM. The drug was applied to the face/scalp in 765 patients (92.7% of all patients) and to the trunk/extremities in 78

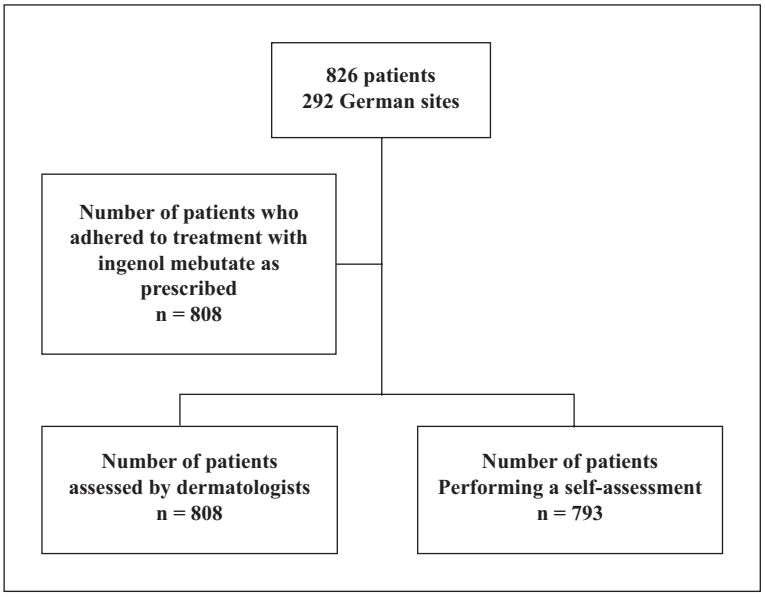

Figure 1. Study design: prospective, open, non-interventional, non-controlled, multicentre study of 826 adult patients with AK enrolled by 292 dermatologists in Germany.

Table 1. Patient characteristics.

	Total population (*n*=826)
Mean age, years (range)	73.2 (28-100)
Sex, *n* (%)	
Male	584 (70.7)
Female	242 (29.3)
Skin type, *n* (%)	
I Always burns easily, never tans	111 (13.5)
II Always burns easily, tans minimally	545 (66.2)
III Burns moderately, tans gradually	152 (18.5)
IV Burns minimally, always tans well	12 (1.5)
V Very rarely burns, tans very easily	3 (0.4)
No data	3
Mean time from initial diagnosis of AK, years (range)	6.2 (0-33)
< 2 years, *n* (%)	136 (16.8)
2-4 years, *n* (%)	253 (31.2)
5-9 years, *n* (%)	212 (26.2)
> 9 years, *n* (%)	209 (25.8)
No data	16
Patients previously treated for AK, *n* (%)	664 (80.4)
Topicals*	305 (46.0)
Cryotherapy*	293 (44.1)
Curettage*	137 (20.6)
Photodynamic therapy*	72 (10.8)
Chemical peeling*	58 (8.7)
Excision*	51 (7.7)
Ablative laser*	38 (5.7)

**The sum of the individual pre-treatments yielded more than 100%, since combinations of pre-treatments were documented.*

Table 2. Characteristics of areas treated with ingenol mebutate.

	Total population (*n*=826)
Anatomical location of AK on head/scalp[#], *n* (%)	765 (92.7)
Forehead[+]	436 (57.0)
Scalp[+]	353 (46.1)
Arms[+]	234 (30.6)
Cheeks[+]	212 (27.7)
Nose[+]	166 (21.7)
Ear[+]	80 (10.5)
Other areas[+]	25 (3.2)
Anatomical location of AK on trunk/extremities[#], *n* (%)	**78 (9.4)**
Dorsum of hands[+]	39 (50.0)
Décolleté[+]	23 (29.5)
Forearm[+]	16 (20.5)
Legs[+]	9 (11.5)
Back[+]	8 (10.3)
Other areas[+]	15 (19.2)

[#]The sum of the anatomical locations yielded more than 100%; in 17 patients (2.1%), both face/scalp and trunk/extremities were treated. [+]The sum of the individual anatomical locations yielded more than 100%; in 450 patients (54.5%), more than one area was treated.

patients (9.4%). In 54.5% patients, more than one area per patient was treated, and in 17 patients (2.1%), IM was used on both the face/scalp and trunk/extremities simultaneously using two different strengths (*table 2*). The size of the treatment areas was on average 21.3±9.6 cm^2 on the face/scalp and 22.7±12.3 cm^2 on the trunk/extremities.

Clearance of AK lesions

Treatment with IM reduced the mean total number of AK lesions per patient significantly from 7.1±6.8 to 2.8±4.5 ($p<0.0001$) (*figure 2A*). This corresponds to a lesion reduction of 60.6%. At Visit 2, complete clearance was achieved in 30.0% of all patients. The mean number of AK lesions on the face/scalp and trunk/extremities

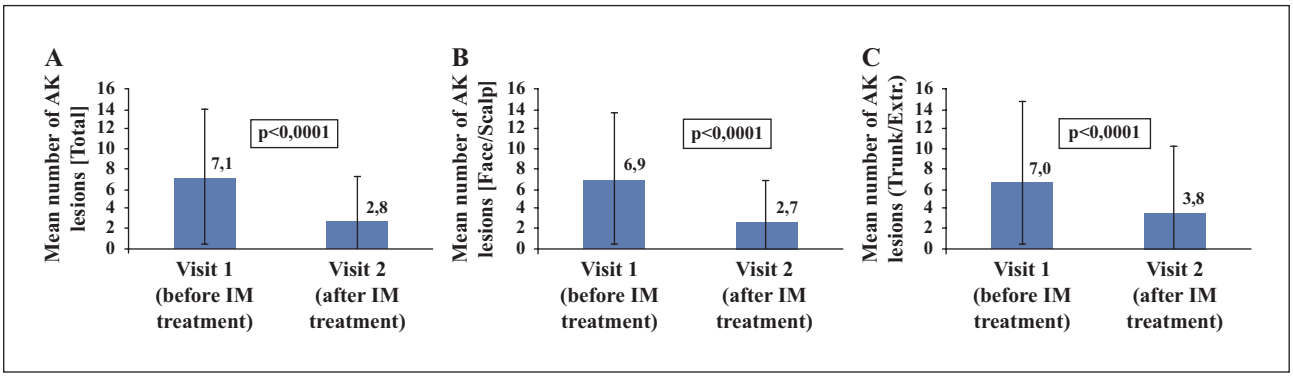

Figure 2. AK lesion reduction in response to ingenol mebutate treatment in all patients (**A**), patients treated on the face/scalp (**B**), and patients treated on the trunk/extremities (**C**).

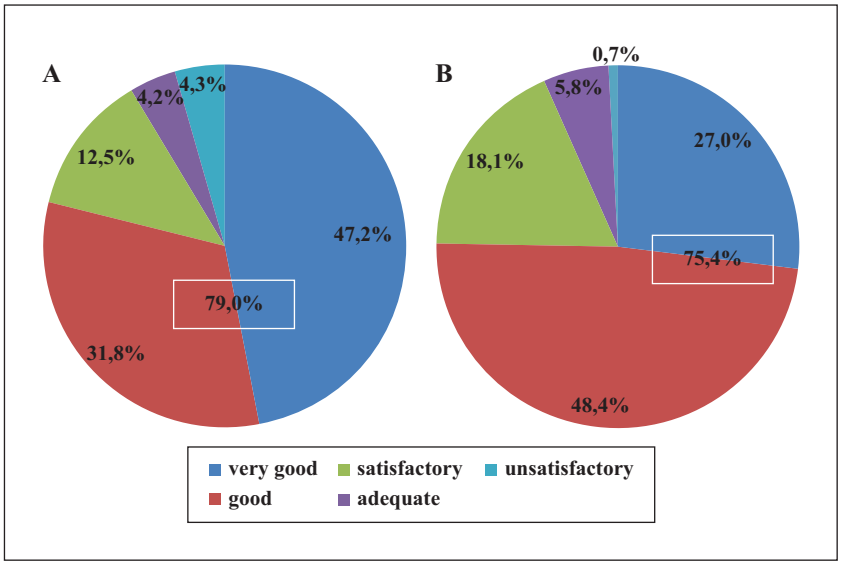

Figure 3. Global assessment of efficacy (**A**) and tolerability (**B**) by dermatologists.

were both significantly reduced from 6.9±6.6 to 2.7±4.1 ($p<0.0001$) (*figure 2B*) and from 7.0±8.1 to 3.8±6.7 ($p<0.0001$) (*figure 2C*), respectively. This corresponds to a lesion reduction of 62.3% for face/scalp and 45.7% for trunk/extremities. At the end of the study, complete clearance was achieved in 31.1% patients with treatment areas on the face/scalp and in 22.2% patients with treatment areas on the trunk/extremities.

Global efficacy and tolerability

At Week 8, IM treatment was assessed by dermatologists in 808 patients. Efficacy was rated "very good"/"good" in 79.0% patients (n=638) and "very good"/"good" tolerability was reported in 75.4% patients (n=609) (*figure 3A, B*).

Adherence

Treatment with IM was followed by 95.8% patients (n=791), as prescribed by dermatologists. Adherence was 97.9% and 88.5% in patients with treatment areas on the face/scalp and trunk/extremities, respectively. In 17 cases (2.1%), no information about adherence was available. Deviations from the prescribed treatment pattern were observed in 18 patients (2.2%), including 12 patients (11 patients with treatment on the face/scalp) with shorter treatment periods due to skin reactions. In three patients, longer treatment intervals were reported (the total number of applications was split over a longer period of time); one patient stopped treatment after hospitalization, one patient received the wrong strength, and in one case no details were available.

Assessment by patients

Treatment satisfaction

At Visit 1, patients were asked about their satisfaction with the last previous AK treatment. In total, 297 of 648 patients (45.8%) were "very satisfied" or "rather satisfied" with previous treatment efficacy; 453 of 623 patients (72.7%) assessed tolerability as "very satisfying" or "rather satisfying"; and 406 of 616 patients (65.9%) were "very satisfied"

Table 3. Patient satisfaction for efficacy, tolerability, and treatment comfort for ingenol mebutate in comparison to the last previous AK treatment.

Patient satisfaction	Efficacy Patients, % (*n*)		Tolerability Patients, % (*n*)		Treatment comfort Patients, % (*n*)	
	Ingenol mebutate	Last previous AK treatment	Ingenol mebutate	Last previous AK treatment	Ingenol mebutate	Last previous AK treatment
Very satisfied	46.0% (365)	15.6% (101)	31.7% (247)	30.7% (191)	41.2% (320)	27.8% (171)
Rather satisfied	36.6% (290)	30.3% (196)	45.1% (352)	42.1% (262)	43.9% (341)	38.2% (235)
A little satisfied	12.1% (96)	39.7% (257)	18.2% (142)	20.6% (128)	11.3% (88)	25.7% (158)
Not satisfied at all	5.3% (42)	14.5% (94)	5.0% (39)	6.7% (42)	3.6% (28)	8.4% (52)

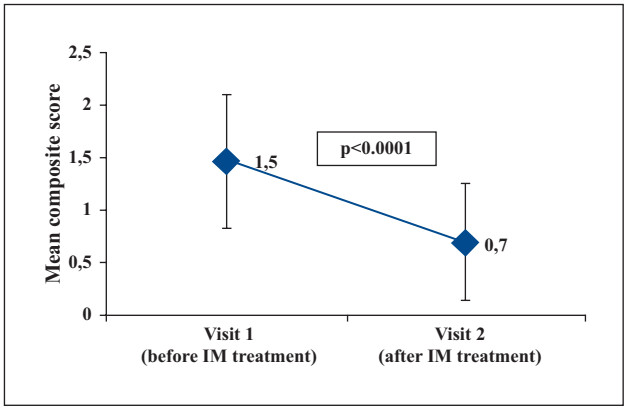

Figure 4. Mean composite score for patient-reported skin conditions.

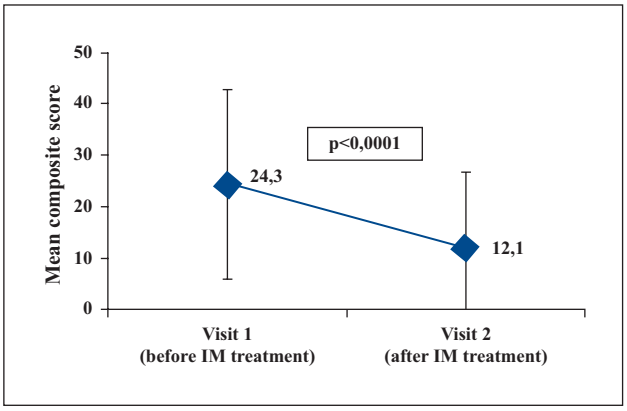

Figure 5. Mean composite score for patient-reported quality of life using the Skindex-16 questionnaire.

or "rather satisfied" with treatment comfort of the last previous AK treatment (*table 3*). Compared to these results, 655 of 793 patients (82.6%) were "very satisfied" or "rather satisfied" with treatment efficacy of IM at Visit 2; 599 of 780 patients (76.8%) were "very satisfied" or "rather satisfied" with tolerability; and 661 of 777 patients (85.1%) were "very satisfied" or "rather satisfied" with treatment comfort of IM (*table 3*).

Skin condition

In total, 274 of 752 patients (36.4%) reported their skin condition as being "a little rough" or "not rough at all" at Visit 1. At Visit 2, significantly more patients reported comparable skin findings (654 of 752 patients, 87.0%; $p<0.0001$). Skin that was "a little wrinkled" or "not wrinkled at all" was reported by 481 of 644 patients (74.7%) at Visit 1, followed by a significant improvement at Visit 2 with 591 of 644 patients (91.8%) reporting skin that was "a little wrinkled" or "not wrinkled at all" ($p<0.0001$). At Visit 1, 344 of 706 patients (48.7%) assessed their skin as "a little blotchy" or "not blotchy at all", which was reported significantly more frequently by patients at Visit 2 (586 of 706 patients, 83.0%; $p<0.0001$). Taken together, the composite score for roughness, wrinkling, and blotchiness from 663 patients indicates that the skin condition improved significantly by 52.7% from 1.5±0.6 points at Visit 1 to 0.7±0.6 points at Visit 2 ($p<0.0001$) (*figure 4*).

QoL

Skin-related QoL data were retrieved from 773 patients using the Skindex-16 questionnaire and revealed a significant improvement of 50.2% between Visit 1 and 2, with a decrease in mean total score (including QoL dimensions such as symptoms, emotions, and functioning) from 24.3±18.4 to 12.1±14.5 ($p<0.0001$) (*figure 5*). In total, 625 of 791 patients (79.0%) would choose treatment with IM again and 61 patients (7.7%) would not; 105 patients (13.3%) could not decide.

Adverse events

In 58 of 826 patients (7.0%), a total of 71 adverse events were reported, as shown in *table 4* (adverse events are only listed if reported more than once). There were no serious adverse events or cases of death. In 15 patients (1.8%) with 22 adverse events, the symptoms had already completely resolved at Visit 2. In six patients (0.7%) with six adverse events, symptoms abated. In 19 patients (2.3%), the adverse events were still remaining at Visit 2. The majority of adverse events (39 adverse events in 31 patients) were of mild intensity. A probable and possible causal relationship with the study drug was reported in 26 patients (3.2%) with 36 adverse events, and in nine patients (1.1%) with 11 adverse events, respectively. No scarring was reported during the observational study period.

Table 4. Adverse events* according to the preferred term in the Medical Dictionary for Regulatory Activities (MedDRA 17.0).

Reported adverse events (AEs)	Patients, % (*n*)
Total number of AEs	7.0% (58)
Lack of efficacy	3.5% (29)
Erythema at the application site	1.0% (8)
Telangiectasia	0.7% (6)
Discolouration	0.7% (6)
Hyperkeratosis	0.4% (3)
Headache	0.2% (2)

**Adverse events were listed if reported more than once.*

Discussion

In this non-interventional study, patients reported a high degree of treatment satisfaction with IM in terms of efficacy, tolerability, and treatment comfort after a follow-up of eight weeks, reflected also by 79.0% of patients who would decide to use this treatment again.

The superiority of patient satisfaction for efficacy and treatment comfort was shown for IM therapy over any last previous treatment. Patient satisfaction for tolerability was similar. We also observed an improvement in skin-related QoL by 50.2%, measured by the Skindex-16 questionnaire. Interestingly, skin-related QoL in our patients seemed to be more severely affected at baseline (mean Skindex-16 score of 24 points) compared to patients with non-melanoma skin cancer (mean Skindex-16 score of 21 points) with improved QoL by 60% after treatment [13].

Pharmacological effectiveness of IM, as evidenced by high AK lesion clearance rates in randomized controlled clinical trials, could make a major contribution to these favourable clinical and patient-reported outcomes [11, 16].

One of the strengths of non-interventional observational studies is that they may provide additional data on patient characteristics, patient-reported outcomes, and treatment effectiveness in a "real-world" setting. In our study, the mean lesion count was significantly reduced on the face/scalp by 62.3% and on the trunk/extremities by 45.7%, but did not reach levels reported in randomized clinical trials with AK lesion reduction rates of 83% and 75%, respectively [11]. A number of reasons for this discrepancy may be proposed, including differences in baseline patient characteristics between the populations investigated. In our study, the majority of treatment areas was located on the forehead and scalp or dorsum of the hands. These locations were described to be more difficult to treat and much less responsive to IM treatment compared to other anatomical sites [17, 18]. The proportion of these patients was about two-fold higher in the current study compared to the randomized trials [11]. We thus consider the high percentage of "difficult-to-treat" sites in our study as a relevant factor that accounts for the mitigated total reduction rate of AK lesions. Of interest, in a recent Phase IV study with Korean AK patients, IM treatment was shown to result in higher complete clearance rates, but also higher LSR scores compared to studies with Western populations. In general, the patient population presented with a predominance of patients with Fitzpatrick skin type III (65.7%). However, the LSR score results may be explained by a weaker skin barrier function in Asian skin [19].

The mean age of our patients was higher (73.2 years) compared to patients in the clinical trials (65.1 years) [11] and hence our patients may have had longer lifetime sunlight exposure (76.5% of our patients had spent their leisure time outdoors for more than 10 years). This could indicate that the skin of our patient population was more severely photo-damaged than that of patients from the randomized clinical trials. On the other hand, the capacity of the immune system to clear damaged cells may be reduced in aged individuals who are more vulnerable to tumours [20].

Permanent skin anomalies were present on the target areas selected for treatment in 26.5% of our patients at baseline (no comparable data are available from other studies), which we considered to be most likely sequelae from preceding surgical and chemical therapies. This suggests that multiple therapeutic attempts had been made to clear the skin that might have been particularly affected by severe and/or recurrent lesions. In our study, 28.2% patients presented with more than eight AK lesions on the target treatment areas. This suggests that a relevant number of patients had been included with a high degree of field cancerization, while in randomized clinical trials, comparable patients (>eight lesions) had been excluded from treatment [11].

Limitations of our study include the non-randomized study design, the relatively short duration of eight weeks follow-up which does not allow conclusions regarding relapse rates, the lack of monitoring of subclinical AK lesions, potential bias in patient-reported outcomes (the assessment of last treatment prior to IM was carried out retrospectively over a long time period), and the interpretation of results based on subjective judgment of the effect, which were not analysed using objective indicators. Another limitation is the study design, in particular, the results of this single-arm study of IM in relation to previous treatments. The comparison with previous treatments is prone to several biases, therefore, conclusions from such a comparison should be drawn with caution. However, a recent head-to-head trial compared the two treatments directly [21].

In randomized clinical trials, considered as the gold standard within the clinical evidence hierarchy, all data relevant to therapeutic interventions in everyday clinical practice cannot be collected for a variety of reasons. Time-limited drug exposure, restricted endpoints, limited sample sizes, and strict inclusion and exclusion criteria all limit the use of the results in a wider context. Non-interventional observational studies, if adequately designed and performed, can add important information from real-world medical practice despite the known inherent limitations, such as non-random assignment, unblinded assessments, and quality limitations of the collected data. Despite these potential limitations, our study has shown that data collected during routine medical practice are consistent with the data obtained under the strict clinical trial conditions of a drug development programme. These types of "real-life" studies are important in confirming the effectiveness and tolerability of newly licensed drugs.

The high adherence rate to IM treatment in our study -nearly all patients adhered to the prescribed treatment- may be considered as another contributing factor to the good treatment outcomes. High adherence rates to treatment may certainly

be attributed to the very short treatment intervals needed with IM. In a recently published observational cohort study (AK-TRAIN) including 1,136 patients who received topical field-directed therapy, patients on long treatment courses were more likely to report difficulties in adhering to AK treatment than patients on IM [22]. The high adherence rate in the present study could also be related to the high proportion of patients with previous AK history and treatment (80%), who were better informed about possible treatment-related side effects. In AK-TRAIN, patients receiving IM benefited from a higher level of communication clarity by improved adherence [22].

Conclusion

IM was highly effective and well tolerated and accepted under "real-world" conditions in patients tending to be more severely affected and with more difficult-to-treat AK lesions relative to randomized clinical trials. Good clinical results in terms of lesion reduction, good patient satisfaction (also relative to the last previous AK treatment), and a significant improvement in skin-related QoL were achieved with IM. Due to the very short treatment periods of two or three days, almost all patients adhered to the prescribed treatment. IM may be considered as a recommendable therapy for AK in the daily clinical setting. ■

Acknowledgement and disclosures. *Ethics statement: All patients provided written informed consent. The research complies with the guidelines for human studies and animal welfare regulations. Approval of the study protocol was obtained from an independent ethics committee (Freiburger Ethikkommission GmbH International). The study was conducted in accordance with the World Medical Association Declaration of Helsinki, and local ethical and legal requirements, such as the guidelines and recommendations of the German Association of Research-based Pharmaceutical Companies (Verband Forschender Arzneimittelunternehmen, VFA) to improve the quality and transparency of non-interventional studies (NIS), the joint recommendations of the Federal Institute for Drugs and Medical Devices (Bundesinstitut fu¨r Arzneimittel und Medizinprodukte, BfArM), and the Paul Ehrlich Institute on planning, conducting and evaluation of post-marketing surveillance studies, as well according to the code of conduct of the Registered Society for Medicinal Products and Cooperation in the Health Sector (Verein Arzneimittel und Kooperation im Gesundheitswesen, AKG e. V.). Acknowledgements: The authors would like to acknowledge Yuri Sankawa for medical writing support that was funded by LEO Pharma in accordance with Good Publications Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). Financial support: This study was supported by LEO Pharma GmbH, Germany. Conflicts of interest: Thomas Diepgen has received honoraria and travelling expenses as consultant and lecturer for LEO Pharma. Christoph Eicke was commissioned by LEO Pharma GmbH for the management of this study. Mike Bastian is an employee of LEO Pharma GmbH. Data management and statistical analyses were performed by Anfomed GmbH, Möhrendorf, Germany.*

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