Dermatologic Therapy

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RESEARCH ARTICLE OPEN ACCESS

Open-Label, Randomized Pilot Study to Evaluate Safety and Tolerability of a Novel Dermal Nanoparticulate Imiquimod Formulation in the Treatment of Actinic Keratosis

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Received: 25 November 2025 | **Revised:** 7 March 2026 | **Accepted:** 19 March 2026

Academic Editor: Yun-Sheng Liang

ABSTRACT

Objective: Actinic keratoses (AKs) are among the most common precancerous lesions in fair-skinned populations and are of considerable clinical relevance. Topical imiquimod has been established as an effective treatment option, although it is associated with local adverse events.

Aim: To assess the tolerability and safety of a novel nanoparticle-based imiquimod formulation (IMI.Gel) for the treatment of AK in comparison to the reference product Aldara. Secondary endpoints included efficacy, cosmetic outcomes, and patient-reported quality of life.

Methods: In an open-label, 1:1 randomized monocentric Phase I/II study patients with clinically diagnosed AK lesions were enrolled. Both groups received topical therapy three times per week over a 4-week period. Efficacy was evaluated at Week 8. In cases of persistent lesions, a second treatment cycle was administered. Follow-up was conducted over a 12-month period with three predefined study visits.

Results: A total of 81 patients were randomized (IMI.Gel $n = 41$; Aldara $n = 40$). The mean age was 72 years (range 44–89), and 78% of participants were male. No statistically significant differences were observed between the two treatment groups regarding tolerability (local skin reactions), safety (adverse events), or efficacy (lesion reduction). A second treatment cycle was performed in 73.0% of patients in the IMI.Gel group and 52.9% in the Aldara group. Complete response rates at 12 months were 48.4% for IMI.Gel and 48.5% for Aldara. Both groups showed a significant improvement in quality of life, as measured by a reduction in the Dermatology Life Quality Index of 1.12 points (IMI.Gel) and 1.02 points (Aldara) after 12 months.

Conclusion: The nanoparticle-based IMI.Gel proved to be a safe and tolerable alternative to the standard therapy with Aldara.

Trial Registration: EudraCT number: 2015-002203-28

Berenice M. Lang and Sophie Luise Meiser contributed equally to this work.

1 | Introduction

Actinic keratoses (AKs) are among the most prevalent dermatological conditions worldwide. Particularly, in individuals with fair skin, AKs are one of the most common manifestations of chronically sun-damaged skin and represent precancerous lesions, thereby constituting a major public health issue with reported prevalence rates ranging from 11% to 25% in various northern hemisphere populations and up to 60% among Australian adults [1–3]. Due to the potential progression of AK to cutaneous squamous cell carcinoma, which carries the risk of metastasis, early, reliable, and effective treatment options are of importance [4, 5]. Various treatment options exist for AK and can broadly be classified into lesion-directed physical therapies (e.g., surgery, cryotherapy, and laser treatment) and field-directed topical therapies (e.g., 5-fluorouracil [5-FU], imiquimod, photodynamic therapy, and tirbanibulin) [6]. When selecting an appropriate therapeutic approach, patient-specific, lesion-specific, and therapy-related factors must be considered [7–9].

One such field-directed treatment option is the commercially available formulation of 5% imiquimod (Aldara), a cream that has proven to be safe and effective against AK. Multiple studies have demonstrated a long-term clinical benefit for the majority of patients, defined as the absence of recurrence of AK lesions in the treatment area [10–13]. The risk of developing a squamous cell carcinoma is significantly reduced after imiquimod treatment even 2 years after therapy [14]. Typically, imiquimod induces a dose-dependent local inflammation, often leading to erythema, pruritus, burning, or pain. These adverse events may negatively impact patient compliance, thereby influencing treatment efficacy and overall therapeutic success [15]. Imiquimod binds specifically to TLR7 and TLR8, receptors expressed on immune cells such as dendritic cells and macrophages. Upon activation, a cascade of innate immune responses is triggered, leading to the production of proinflammatory cytokines, such as IFN-α, TNF-α, and IL-6 [16]. While the precise mechanism of action of imiquimod in AK patients is not fully understood, it can be assumed that the long-term benefit may result from stimulation of immune memory through cell-mediated antitumor pathways [17].

IMI.Gel is a semisolid formulation containing nanoparticulate imiquimod 5% and was initially developed as a vaccine adjuvant for transcutaneous immunization [18–20]. Although the dosage of imiquimod in IMI.Gel is identical to that in the commercially available formulation Aldara, the two products differ in their overall composition as well as in their additional constituents. Preclinical studies have shown that the consistency and additional constituents may influence the effectiveness of different imiquimod-based creams [21]. Nonclinical studies in mice conducted by our group supported the hypothesis that the newly developed imiquimod formulation induces equal or improved outcomes, as demonstrated in skin permeation and penetration tests as well as in the induction of an immune response, compared with the branded product [20]. In mice, cytotoxic T-cell responses induced by imiquimod-based transcutaneous immunization using the commercial formulation rapidly fade, resulting in poor memory formation and only partial tumor protection. In contrast, the newly introduced composition of IMI.Gel has shown longer-lasting effects in mice. Furthermore, IMI.Gel is devoid of isostearic acid, a contributor to Aldara-induced local skin reactions, which could be beneficial with regard to the adverse event profile [11].

2 | Aim

In this first-in-human Phase I/II study, we aimed to compare a newly developed nanoparticulate formulation, IMI.Gel, with the commercially available Aldara cream for the treatment of AK, focusing on safety and tolerability as primary endpoints. Additionally, efficacy, cosmetic outcomes, and quality of life (QoL) were assessed as secondary endpoints.

3 | Materials and Methods

This was an open-label, randomized Phase I/II study evaluating the safety and tolerability of a novel nanoparticulated imiquimod formulation compared with Aldara for the treatment of AK at a single academic study center. Patients were enrolled from February 2019 to April 2023 at the outpatient clinic of University Medicine Mainz, Department of Dermatology. The last follow-up data were collected in April 2024.

The investigational product, IMI.Gel, is an emulsion hydrogel containing 5% nanoparticulate, suspended imiquimod (the composition has been published elsewhere [22]). It was manufactured at the Institute of Pharmaceutical and Biomedical Sciences at the University of Mainz. The formulation, production, and storage of IMI.Gel were carried out following pharmaceutical standard processes and Good Manufacturing Practice procedures.

For study inclusion, a confirmed clinical diagnosis of AK (Olsen I–III) with at least two distinct AK lesions was required. Eligible participants were 18 years or older and had an ECOG performance status of 0–1. Women of childbearing potential were required to present a negative serum pregnancy test at screening and to commit to using a highly effective contraceptive method throughout the study period. Furthermore, all participants were required to provide written informed consent before undergoing any study-related procedures.

Exclusion criteria included any previous treatments in the affected region within the past 2 months, including topical therapies with imiquimod, diclofenac, ingenol mebutate, 5-FU, salicylic vaseline, steroids, or retinoids, as well as photodynamic therapy, UVA/UVB/PUVA therapy, laser abrasion, dermabrasion, or chemical peels. The use of moisturizers in the treatment area was prohibited to avoid masking the effects of imiquimod through mere skin barrier hydration status. Patients with therapy-refractory AKs or those who have undergone surgery in the treatment area were not eligible for inclusion. Additionally, individuals with a history of basal cell carcinoma, Bowen's disease, or squamous cell carcinoma within the past 2 years were excluded. Further exclusion criteria included systemic steroid use within the last 4 weeks (except for inhaled or nasal steroids up to 1200 μg/day of beclomethasone), immunosuppressive drugs such as steroids, interferon, azathioprine, or cyclosporine, and any participation in another clinical trial within the past 3 months. Patients with a known hypersensitivity to imiquimod or any of the study additives or a history of HIV, hepatitis B, or hepatitis C infection were also excluded. Furthermore, individuals with malignant tumors other than those previously mentioned, severe neurological or mental disorders interfering with their ability to give informed consent, or a history of organ transplantation were ineligible. Finally, pregnant or lactating individuals were excluded from participation.

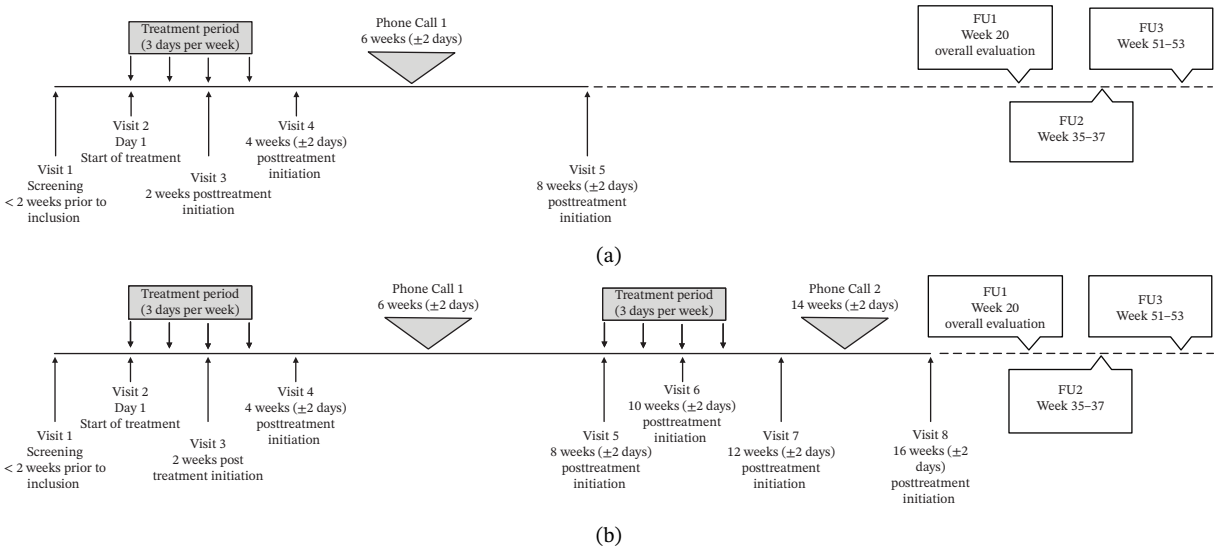


FIGURE 1 | (a) Overview of study visits for patients with complete response at Visit 5, i.e., patients receiving only one treatment cycle (FU = follow-up visit). (b) Overview of study visits for partial or nonresponding patients at Visit 5, i.e., patients receiving two treatment cycles.

Patients were randomized in a 1:1 ratio to receive Aldara or IMI.Gel. Treatment was administered according to the Aldara label, three times a week for 4 weeks. The randomization schedule was generated by the Institute of Pharmacy, and block randomization was used. Assessments were performed four and 8 weeks after initiation of treatment with the possibility of an additional treatment cycle if AK lesions were still present. Follow-up was conducted at three time points within 12 months (Figure 1). Patients were required to discontinue the treatment if they experienced treatment-related adverse events > Grade 2 according to CTCAE or if they were noncompliant, defined as taking less than 60% of the scheduled doses.

The primary endpoint was tolerability, assessed using the local skin reaction (LSR) score with erythema rating (ER; *none* = 0, *mild* = 1, *moderate* = 2, and *severe* = 3) as the main criterion. Additional criteria included other skin reactions (edema, exudate, vesicles, erosions, ulcerations, scaling, and scabbing; rating 0–3). Secondary endpoints were safety, efficacy, compliance, cosmetic outcome, and QoL. Safety was analyzed by measurement of vital signs and recording of adverse events according to CTCAE 4.0. Treatment efficacy was indicated by AK lesion clearance rate (absolute and area). Compliance was documented in a personal dosing diary and by the return of unused study medication. Cosmetic outcome was evaluated using skin quality assessment (skin surface, hyperpigmentation, hypopigmentation, irregular pigmentation, and skin atrophy, each scale 0–3), physician global assessment (scale 0–4), and patient global assessment (scale 0–4). The evaluating physicians were board-certified dermatologists with extensive experience as study investigators and were therefore familiar with the applied scoring systems. Whenever possible, assessments were performed by the same investigator to reduce interobserver variability. Data on QoL were collected using the Dermatology Life Quality Index (DLQI) [23]. Photographs were taken at each visit. Demographic data were collected.

Ethical approval was obtained from the Ethics Committee of Rhineland-Palatinate as well as the Federal Institute for Drugs and Medical Devices in Germany (BfArM). The study was registered at EudraCT (2015-002203-28) and conducted in accordance with the Declaration of Helsinki. All patients provided oral and written informed consent after being informed by the study physicians.

Statistical analyses and data visualizations were performed using the R programming language (Version 4.4.0; R Core Team, 2025). Data preprocessing and manipulation were performed using packages from the tidyverse ecosystem, including dplyr, tidyr, stringr, and purrr. Visualizations were created with ggplot2 and enhanced using ggbreak. For statistical modeling and inference, the packages emmeans, lmtest, nortest, MASS, pscl, and car were used.

Tolerability was primarily assessed using the ER (0–3) in the safety analysis set (SAF). Analyses were performed using available-case data, and corresponding results based on a Last Observation Carried Forward (LOCF) dataset were reported alongside to allow assessment of robustness. The proportions of patients of the two treatments showing ER ≥ 2 versus < 2 were compared using a one-sided Fisher's exact test 4 weeks after the last treatment, as prespecified in the study protocol. An exploratory Mann–Whitney *U* test (across all ratings 0–3) was additionally performed.

LSR scores (0–3) assessed in addition to ER were analyzed descriptively in the SAF using available-case data. Results were summarized and presented graphically.

The skin quality assessment (ordinal composite score, calculation shown in Figure S3) was evaluated in the full analysis set (FAS). Analyses were based on complete-case data with corresponding LOCF imputed results provided to illustrate robustness. Ordinal logistic regression was applied to compare the cosmetic outcome ratings between treatment groups at baseline and follow-up visits as prespecified in the study protocol. Ratings were coded on an ordinal scale from 0 ("*very good*") to 4 ("*impaired*"), with higher values indicating worse cosmetic results. IMI.Gel was coded as 0 and Aldara as 1. Thus, odds ratios > 1

indicate higher odds of a worse cosmetic outcome for Aldara relative to IMI.Gel. The global assessment (ordinal variable on a scale 0–4) rated by the investigator and the patient at baseline and follow-up visits was analyzed in the FAS population using available-case data and presented descriptively.

Lesion count and clearance assessed at follow-up visits (clearance as a binary variable for individual lesion [cleared or not cleared]) were analyzed in the FAS population using available-case data and additionally after nonresponder imputation for missing postbaseline values. Negative binomial regression was performed with treatment as the only factor according to the study protocol. In the negative binomial model, IMI.Gel was coded as 0 and Aldara was coded as 1. Therefore, positive estimates and rate ratios (RRs) > 1 indicate fewer lesions under IMI.Gel compared with Aldara. Lesion area was summarized descriptively in the FAS (available-case data). Lesion area reduction was analyzed using ANCOVA with the baseline lesion area as a covariate according to the study protocol. For robustness, the same analysis was performed using baseline values carried forward if all postbaseline values were missing.

The DLQI score was analyzed in the FAS using complete-case data. Paired *t*-tests within treatment groups were applied to compare baseline values with those at the last follow-up visit.

Repeated measures were summarized descriptively across visits. For inferential analyses, a single postbaseline value per patient was selected using visit-prioritization rules which were predefined in the study protocol (e.g., 4 weeks after the last treatment for ER, 4 weeks after the last treatment for lesion area, and follow-up visits for skin quality assessment [according to calculation shown in Figure S2]). No formal multiplicity adjustment was applied across endpoints or time points. The study included one predefined primary endpoint (ER 4 weeks after the last treatment), and all other endpoints were exploratory or supportive. Consequently, p values for these analyses were not adjusted for multiplicity and should be interpreted as descriptive.

The graphical elements in this article were designed using Adobe Illustrator and Microsoft Visio.

4 | Results

4.1 | Patient Population

A total of 82 patients were enrolled in the study; 81 patients were randomized to treatment (IMI.Gel $n = 41$; Aldara $n = 40$), whereas 39 patients ultimately started treatment with IMI.Gel and 34 patients with Aldara. Almost all patients treated with IMI.Gel (94.9%) and all patients treated with Aldara (100.0%) completed the study until the primary endpoint in Week 8 (visit 5). 90.1% of patients who reached the primary endpoint completed 1-year follow-up. A total of 27 patients in the IMI.Gel group (69.2%) and 18 patients in the Aldara group (52.9%) underwent a second treatment cycle due to remaining lesions at Visit 5 (Figure 2). Among the 81 randomized patients, 63 (77.8%) were male with a mean age of 72 years (range: 44–89). Skin types according to the Fitzpatrick scale were distributed as follows: 17.6% Type I, 75.3% Type II, and 1.2% Type III. The distribution was balanced between treatment groups. The predominant tumor location was the face (59.4%), followed by the scalp (20.6%) and the upper extremity (10.6%) (Table 1).

4.2 | Tolerability and Safety

LSR was evaluated at each visit with highest values at Visit 4 (4 weeks posttreatment initiation). On average, erythema was rated as mild to moderate in both treatment groups, while edema, exudation, vesiculation, erosion, ulceration, scabbing, and flaking were rated as none to mild. For the primary tolerability endpoint, the ER 4 weeks after the last treatment was evaluated. The Mann–Whitney-U test showed no evidence of a difference between the IMI.Gel and the Aldara groups ($W = 663.5$; $p = 0.9904$). After LOCF imputation, the trend of the results remained unchanged ($W = 659.5$; $p = 0.9710$). Effect size estimates confirmed the absence of a meaningful effect, as the Hodges–Lehmann estimator showed a median difference close to zero (−0.00003; 95% CI [−0.000057, 0.000008]), and Cliff's delta indicated a negligible effect ($\delta = -0.0023$; 95% CI [−0.245, 0.241]). The same findings were observed after LOCF imputation (HL = −0.00003; 95% CI [−0.000043, 0.000004]; $\delta = -0.0053$; 95% CI [−0.247, 0.237]). The one-sided Fisher's exact test (ER ≥ 2 versus < 2) was prespecified in the study protocol but was only of limited value due to unexpectedly low ER in both treatment groups (OR = 0.2078; 95% CI [0.0087, inf.]; $p = 0.9819$; after LOCF imputation: OR = 0.2745; 95% CI [0.0111, inf.]; $p = 0.9603$). At the time of the primary endpoint (Week 8, Visit 5), LSR values had decreased to none or mild on average for all study participants in both treatment groups. Interpretation of the LSR over time, therefore, focused on the descriptive plots due to the limited reliability of inferential analyses of the zero-inflated variables (Figure 3, Figure S1).

Throughout the study, eight serious adverse events (SAEs) occurred, corresponding to an SAE rate of 10.96%. None of these events were related to the treatment. Three patients in the IMI.Gel group and five patients in the Aldara group experienced SAEs (Table S1). No new adverse events of special interest were observed in either treatment group. In one patient in the Aldara group, systemic adverse events with fever and facial swelling were documented at Visit 3 (CTCAE Grade 1). The patient discontinued treatment after the first treatment cycle but remained in the study. One patient in the IMI.Gel group discontinued treatment due to itching at the treated skin area (CTCAE Grade 1) during the first treatment cycle and subsequently terminated participation in the study early (Figure 2).

Compliance was assessed based on diary entries and the quantity of returned study medication. Adherence was comparable between both study arms and remained consistently high. Only one patient in the IMI.Gel group was excluded from the study due to noncompliance (defined as < 60% of all scheduled administrations) (Figure 2).

4.3 | Efficacy

Complete response rates after one cycle (Visit 5) were 25.6% in the IMI.Gel group and 47.1% in the Aldara group. After 12 months, complete response rates were 48.4% for IMI.Gel and 48.5% for Aldara. There were 25.8% nonresponders and 25.8% partial responders in the IMI.Gel group and 27.3% and 24.2% in the Aldara group, respectively (Table 2). Negative binomial regression of the mean number of lesions at follow-up did not provide evidence for a treatment effect (estimate 0.061, 95% CI [−0.25, 0.37], $p = 0.702$). The corresponding RR for the Aldara versus IMI.Gel group was 1.06 (95% CI [0.78, 1.45]). A likelihood-

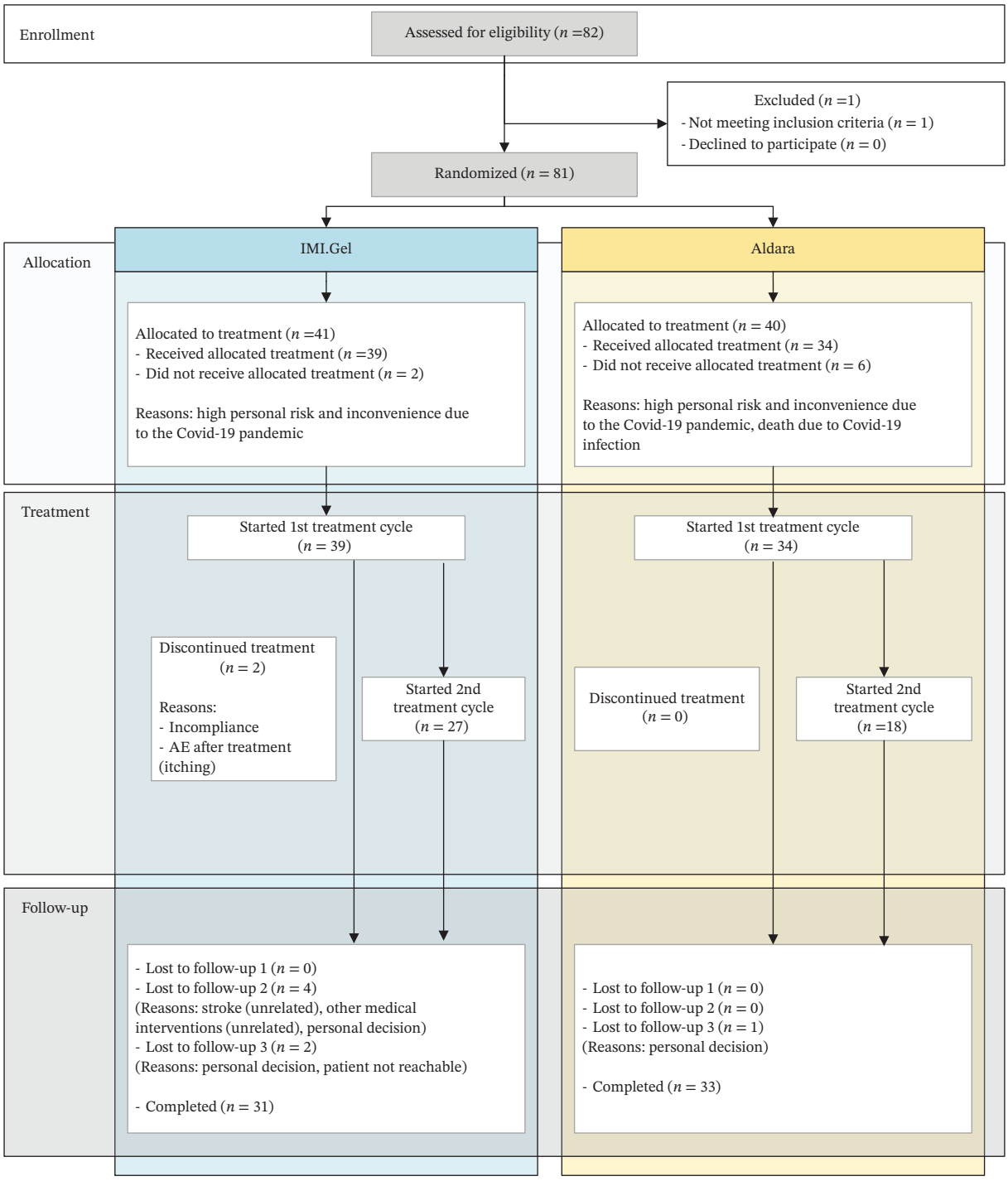


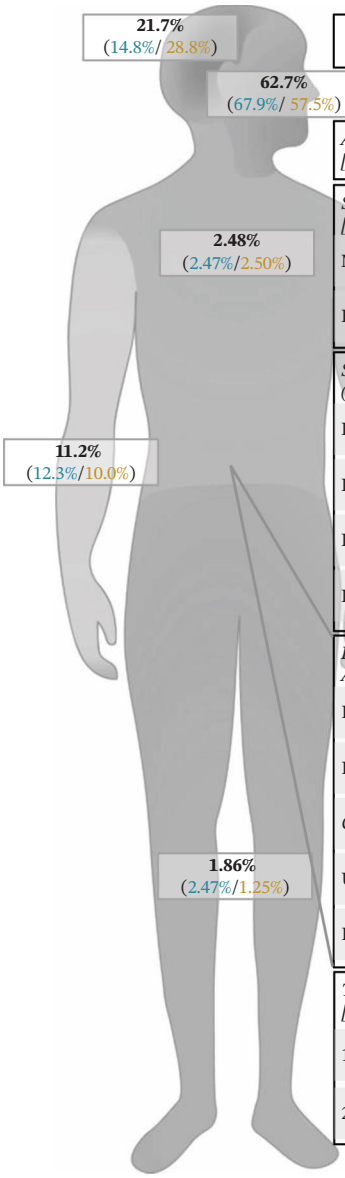
FIGURE 2 | Flow diagram of participant progress through the trial.

ratio test confirmed the absence of a treatment difference with respect to the lesion count at follow-up ($\chi^2 = 0.146$, $p = 0.702$). After missing data imputation, the direction of the treatment effect remained unchanged, and the results continued to show no evidence of a treatment effect (estimate 0.167, 95% CI [−0.12, 0.46], $p = 0.258$; RR 1.18, 95% CI [0.89, 1.59]; LR $\chi^2 = 1.28$, $p = 0.258$). Although the estimates differed between the analyses, both indicated the absence of a statistically significant treatment effect.

Given the observed numerical difference in the number of patients requiring a second treatment cycle in the IMI.Gel group compared with the Aldara group, an exploratory subgroup analysis of patients who received only one treatment cycle was performed. The results did not indicate a different trend compared with the analysis of the whole study population (including patients receiving either one or two treatment cycles) (estimate 0.222, 95% CI [−0.59, 1.04], $p = 0.594$; RR 1.25, 95% CI [0.55, 2.82]; LR $\chi^2 = 0.28$, $p = 0.594$). However, due to the difference in population size between the groups, these results should be interpreted with caution.

The mean lesion area of the patients at the baseline visit was $1.58 \pm 2.63\,cm^2$ in the IMI.Gel group and $1.38 \pm 1.08\,cm^2$ in the

TABLE 1 | Patient characteristics of study population ($n = 81$).



Study population	IMI.Gel	Aldara	Total
Age [years (range)]	71 (44–84)	73 (57–89)	72 (44–89)
Sex [n (%)]			
Male	30 (73.2)	33 (82.5)	63 (77.8)
Female	11 (26.8)	7 (17.5)	18 (22.2)
Skin type (Fitzpatrick scale) [n (%)]			
I	8 (20.0)	7 (17.5)	15 (18.8)
II	31 (77.5)	33 (82.5)	64 (80.0)
III	1 (2.50)	0 (0.0)	1 (1.25)
IV-VI	0 (0.0)	0 (0.0)	0 (0.0)
Location of treated AK lesion [n (%)]			
Face	55 (67.9)	46 (57.5)	101 (62.7)
Head	12 (14.8)	23 (28.8)	35 (21.7)
Chest	2 (2.47)	2 (2.50)	4 (2.48)
Upper extremities	10 (12.3)	8 (10.0)	18 (11.2)
Lower extremities	2 (2.47)	1 (1.25)	3 (1.86)
Treatment cycles [n (%)]			
1	10 (27.0)	16 (47.1)	26 (36.6)
2	27 (73.0)	18 (52.9)	45 (63.4)

Note: Mean values are presented in bold (IMI.Gel/Aldara).

Aldara group. At Follow-Up 1, the mean lesion area was 0.289 $\pm$ 0.47 cm^2 in the IMI.Gel group and 0.393 $\pm$ 0.67 cm^2 in the Aldara group, corresponding to an average lesion reduction of 74.3 $\pm$ 41.7% for IMI.Gel and 80 $\pm$ 29.01% for Aldara (Figure 4). ANCOVA indicated a numerically greater lesion area reduction in the Aldara group (adjusted mean difference Aldara–IMI.Gel: 11.5% points; 95% CI [-1.6, 24.6]), although this difference was not statistically significant ($p = 0.085$). After missing data imputation, the adjusted mean difference (Aldara–IMI.Gel) was 8.3% points (95% CI [−4.3, 20.9]; $p = 0.1946$). A subgroup analysis of patients receiving only one treatment cycle indicated higher lesion reduction for both treatment groups (at Follow-Up 3: 89.3 $\pm$ 26.8% for IMI.Gel and 93.9 $\pm$ 16.9% for Aldara). However, given the small and unbalanced subgroup sizes, these findings are exploratory and should not be overinterpreted. The observed trend toward higher lesion reduction in patients receiving fewer treatment cycles may suggest that early responders continue to show better efficacy, although it more likely reflects individual response patterns rather than differences between the treatments.

4.4 | Cosmetic Outcome

Cosmetic outcome was evaluated using global assessment scores from both physicians and patients, as well as changes in skin quality assessment. Global assessment scoring showed very good or good outcomes after 12 months in 78.7% of patients in the IMI.Gel group and 67.8% in the Aldara group when rated by investigators, and 75.0% and 59.3% of patients, respectively, when rated by patients (Figure S2). As this evaluation may be influenced by subjective bias from both investigators and the patients, cosmetic outcome was additionally assessed using a composite score derived from the skin quality assessment. Changes in skin quality were calculated as described in Supporting Information using the following skin parameters at baseline and follow-up

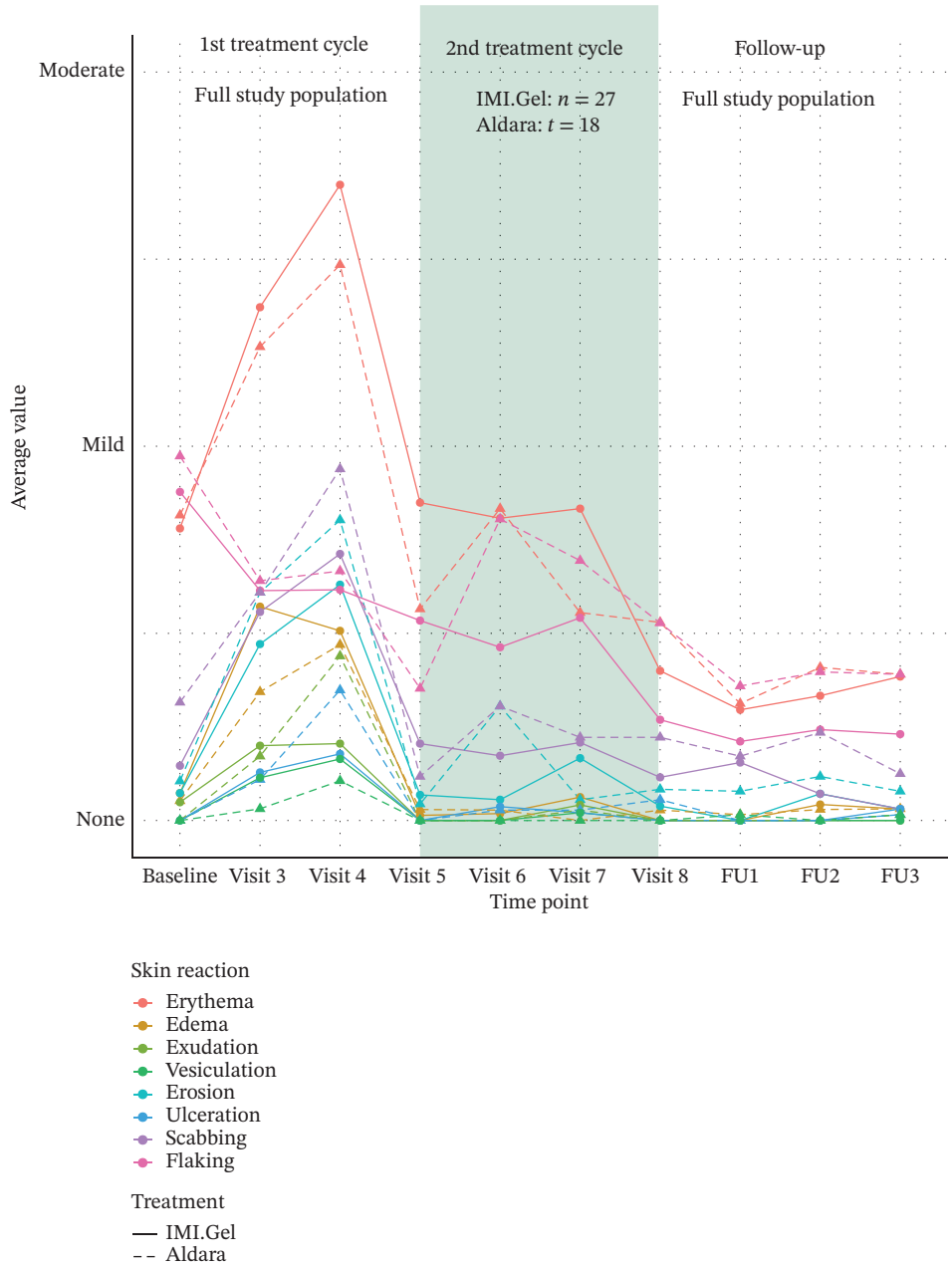


FIGURE 3 | Safety assessment via LSR with erythema as the most common response in both study groups, showing means of the variables per visit.

visits: skin surface, hyperpigmentation, hypopigmentation, mottled or irregular pigmentation, degree of scarring, and atrophy (Figure S3). Ordinal logistic regression of the calculated skin quality scoring revealed that treatment with Aldara was significantly associated with poorer cosmetic outcomes compared with treatment with IMI.Gel at the first follow-up visit. In detail, the odds of a worse cosmetic outcome score in the Aldara group at Follow-Up 1 were 3.16 times higher than in the IMI.Gel group (OR = 3.16, $p = 0.0179$, 95% CI [1.22, 8.15]; after missing data imputation: OR = 3.07, $p = 0.0142$, 95% CI [1.25, 7.52]), and at Follow-Up 2, 2.91 times higher (OR = 2.91, $p = 0.0293$, 95% CI [1.12, 7.63]; after missing data imputation: OR = 2.44, $p = 0.0502$, 95% CI [1.00, 5.98]). At Follow-Up 3, a similar trend was observed (OR = 2.29, 95% CI [0.85, 6.18]), although the effect was not showing statistical significance ($p = 0.0989$; after missing data imputation: OR = 2.04, $p = 0.118$, 95% CI [0.84, 4.96]) (Figure 5(a)).

4.5 | QoL

QoL was evaluated using the DLQI at baseline and at Follow-Up 3. Before treatment, the mean DLQI was 2.15 in the IMI.Gel group and 2.03 in the Aldara group, reflecting a small impact on QoL. Both groups showed a significant improvement, demonstrated by a reduction in DLQI of 1.12 points (95% CI: 0.07–2.17; $p = 0.036$) (IMI.Gel) and 1.02 points (95% CI: 0.25 - 1.80; $p = 0.011$) (Aldara) after 12 months. At the end of the study, 80.5% of patients in the IMI.Gel group and 80.0% of patients in the Aldara group presented with a DLQI score of 0 or 1, indicating that the disease—AK—had no impact on QoL (Figure 5(b)).

5 | Discussion

This randomized, investigator-initiated Phase I/II pilot study represents the first clinical evaluation of a novel nanoparticulate

TABLE 2 | Complete response rates as observed in follow-up visits.

Treatment cycles	IMI.Gel				Aldara			
	Follow-Up 1							
	Nonresponder (*n* (*n*/*N* [%]))	Partial responder (*n* (*n*/*N* [%]))	Complete responder (*n* (*n*/*N* [%]))	∑	Nonresponder (*n* (*n*/*N* [%]))	Partial responder (*n* (*n*/*N* [%]))	Complete responder (*n* (*n*/*N* [%]))	∑
1	1 (2.7%)	1 (2.7%)	8 (21.6%)	10	2 (6.1%)	3 (9.1%)	10 (30.3%)	15
2	7 (18.9%)	9 (24.3%)	11 (29.7%)	27	8 (24.2%)	4 (12.1%)	6 (18.2%)	18
∑	8 (21.6%)	10 (27.0%)	19 (51.4%)	$N = 37$	10 (30.3%)	7 (21.2%)	16 (48.5%)	$N = 33$
	Follow-Up 2							
	Nonresponder (*n* (*n*/*N* [%]))	Partial responder (*n* (*n*/*N* [%]))	Complete responder (*n* (*n*/*N* [%]))	∑	Nonresponder (*n* (*n*/*N* [%]))	Partial responder (*n* (*n*/*N* [%]))	Complete responder (*n* (*n*/*N* [%]))	∑
1	1 (3.0%)	1 (3.0%)	5 (15.2%)	7	2 (5.9%)	5 (14.7%)	9 (26.5%)	16
2	9 (27.3%)	5 (15.2%)	12 (36.4%)	26	6 (17.6%)	6 (17.6%)	6 (17.6%)	18
∑	10 (30.3%)	6 (18.2%)	17 (51.5%)	$N = 33$	8 (23.5%)	11 (35.3%)	15 (44.1%)	$N = 34$
	Follow-Up 3							
	Nonresponder (*n* (*n*/*N* [%]))	Partial responder (*n* (*n*/*N* [%]))	Complete responder (*n* (*n*/*N* [%]))	∑	Nonresponder (*n* (*n*/*N* [%]))	Partial responder (*n* (*n*/*N* [%]))	Complete responder (*n* (*n*/*N* [%]))	∑
1	1 (3.2%)	1 (3.2%)	5 (16.1%)	7	1 (3.0%)	4 (12.1%)	11 (33.3%)	16
2	7 (22.6%)	7 (22.6%)	10 (32.3%)	24	8 (24.2%)	4 (12.1%)	5 (15.2%)	17
∑	8 (25.8%)	8 (25.8%)	15 (48.4%)	$N = 31$	9 (27.3%)	8 (24.2%)	16 (48.5%)	$N = 33$

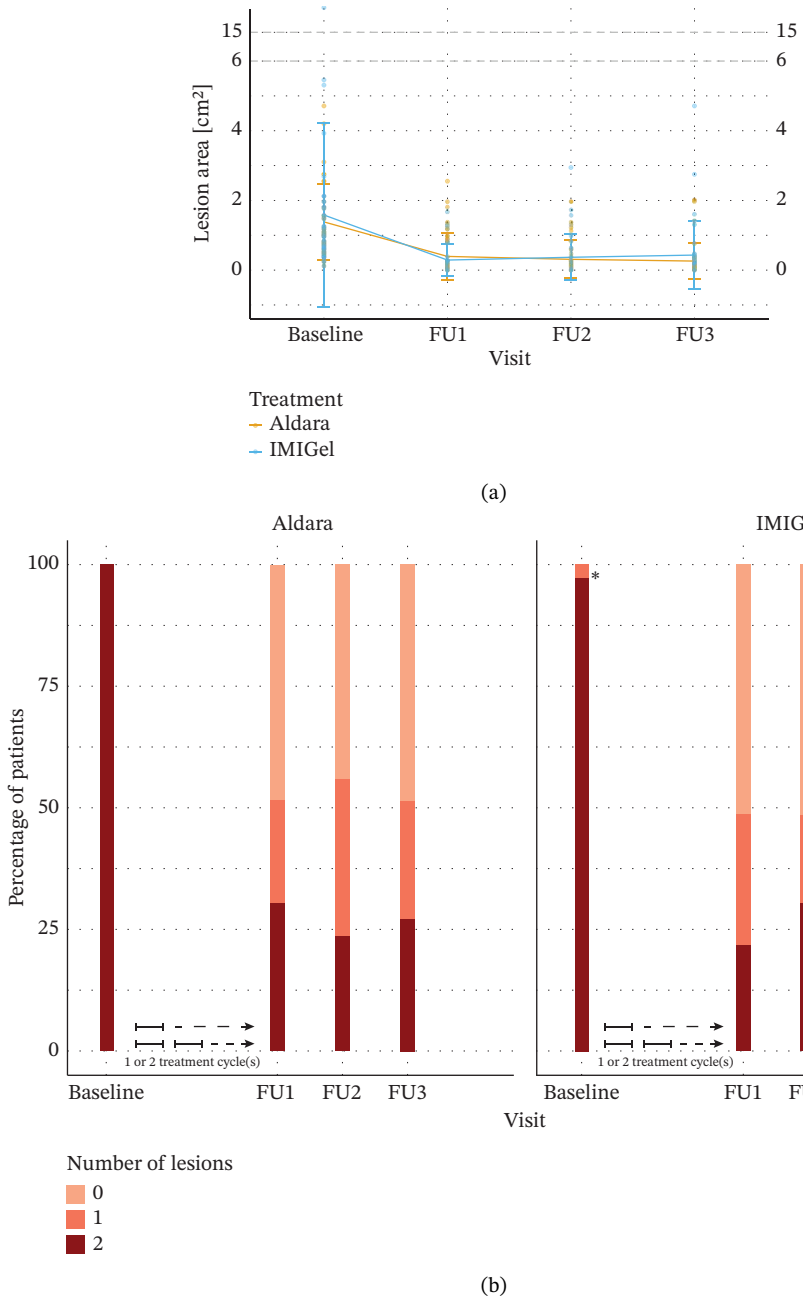
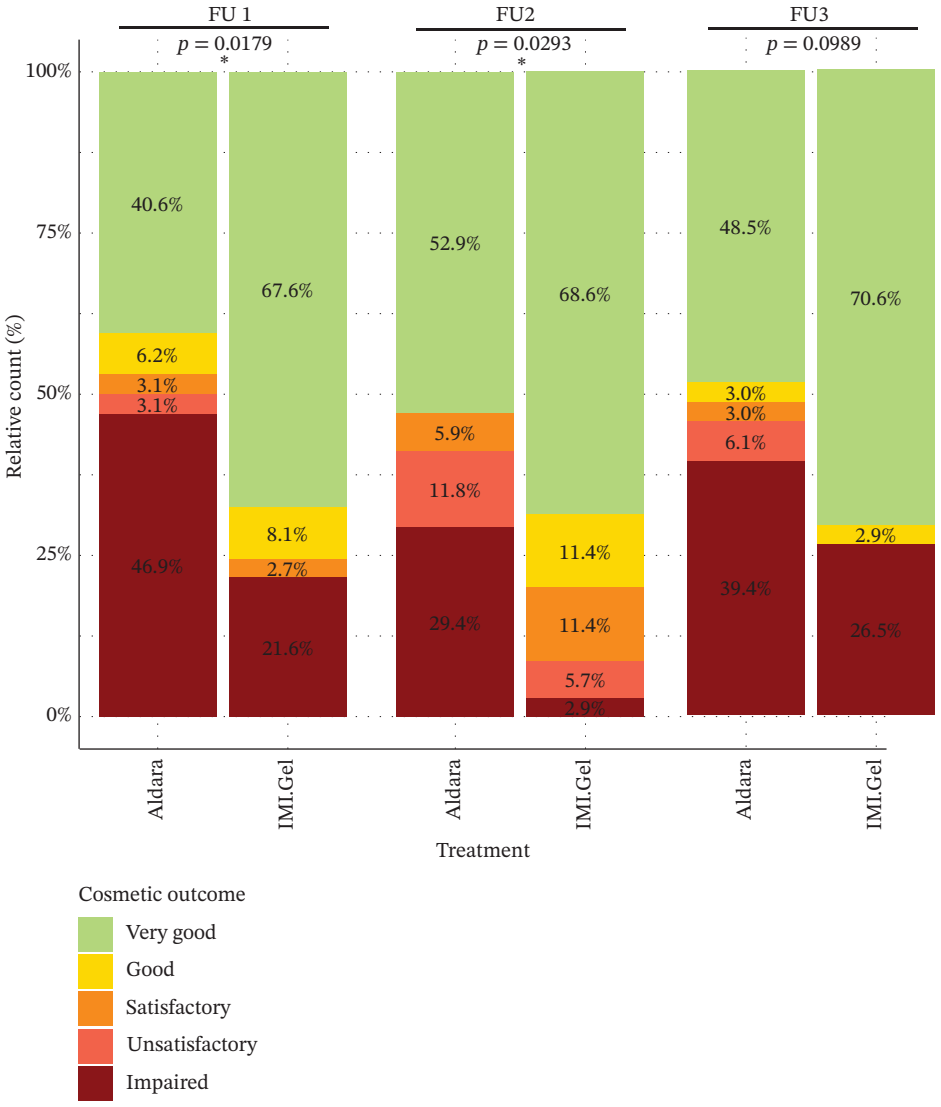


FIGURE 4 | (a) Average lesion area (arithmetic mean ± SD in cm^2) throughout the study visits. (b) Average number of detectable lesions throughout the study visits (percentage of patients with 0, 1, or 2 lesions). One patient had only one AK lesion at baseline visit.

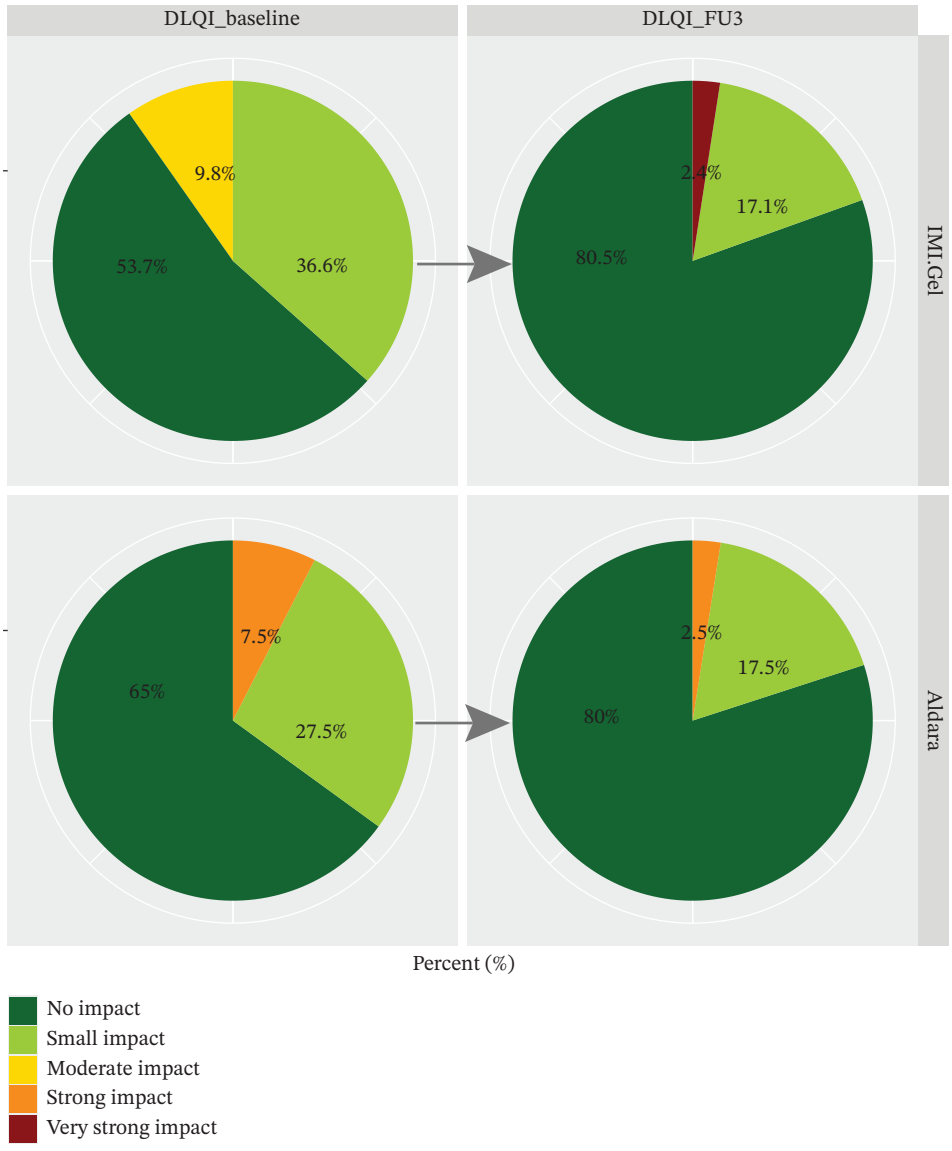
5% imiquimod formulation (IMI.Gel) in comparison with the established commercial product Aldara for the topical treatment of AK. As a pilot randomized comparative tolerability study, the primary objective was to explore safety and local tolerability while generating preliminary signals regarding clinical performance. Within this exploratory framework, IMI.Gel demonstrated an acceptable safety profile and was generally well tolerated. The study was not designed, powered, or statistically structured to determine comparative efficacy, equivalence, or noninferiority between formulations.

Our study population aligns with the typical demographic profiles of AK patients reported in the literature concerning age and gender distribution; of note, it predominantly includes patients with Fitzpatrick skin Types I and II. However, in contrast to previous research, including pivotal clinical trials, we deliberately did not restrict tumor localization solely to the face and scalp [10–13]. In contrast, we incorporated a broader range of anatomical sites, encompassing more challenging localizations such as the extremities. Furthermore, our inclusion criteria extended to patients classified as Olsen Stages I through III, thereby covering a spectrum of disease severity that exceeds that typically addressed in approval studies. While this broader inclusion enhances clinical applicability, it also reinforces the exploratory nature of efficacy observations, which should be interpreted cautiously in the absence of confirmatory statistical powering.



(a)

FIGURE 5 | (Continued)



(b)

FIGURE 5 | (a) Cosmetic outcomes rated by the investigators across study visits and treatment groups, based on the calculated changes in skin quality assessment (see Figure S3 for calculation). (b) Impact of AK on QoL: Percentage frequency of DLQI scores at baseline (left) and at the end of the study after 12 months (right) for IMI.Gel (top) and Aldara (bottom) (calculated from the DLQI questionnaires for patients).

Tolerability, our predefined primary endpoint, was overall good in both treatment groups. Descriptively, fewer local adverse events such as ulceration and exudation were observed in the IMI.Gel arm, although a second treatment cycle was required more frequently. Patients reported favorable treatment comfort, but given the pilot character of the study and the limited sample size, these observations should be interpreted as preliminary. On the one hand, the study was not blinded; therefore, patients may have been subject to expectation bias. On the other hand, observed differences may plausibly relate to formulation characteristics. Aldara is a vaseline-based lotion in which the active pharmaceutical ingredient, imiquimod, is fully dissolved and combined with isostearic acid, a known penetration enhancer. While this promotes rapid dermal absorption, it may lead to systemic spread, loss of localized drug retention, and an increased incidence of adverse events such as pruritus, burning, and erythema [24]. In contrast, IMI.Gel is based on a hydrophilic polyacrylate gel incorporating a dispersed lipophilic phase (jojoba oil), in which the active pharmaceutical ingredient remains in a nanodispersed crystalline state. Nanomilling allows for efficient skin penetration of imiquimod in solid form, promoting localized, sustained drug release, thereby potentially reducing the risk of systemic exposure and associated adverse events [20]. However, mechanistic explanations remain theoretical within the context of this clinical pilot and were not directly tested. Additionally, the use of jojoba oil, a cosmetically well-tolerated natural excipient, may improve skin compatibility and potentially support the healing of keratotic lesions by softening crusted plaques and enhancing skin barrier recovery. Whether these formulation attributes translate into clinically meaningful tolerability advantages requires confirmation in adequately powered, blinded trials.

Cosmetic outcomes were assessed as secondary, exploratory endpoints. Both investigators and patients descriptively rated posttreatment skin appearance favorably in the IMI.Gel group during follow-up. However, interpretation is limited by the open-label design and the subjective nature of cosmetic assessments, which are particularly susceptible to expectation and observer bias. Consequently, these findings should be considered hypothesis-generating only. Cosmetic endpoints are increasingly recognized as relevant in AK field therapy, especially in cosmetically sensitive areas, but require rigorous blinded evaluation [7–9, 25–28].

With regard to efficacy, both study arms demonstrated clinical activity consistent with the known therapeutic effects of topical imiquimod. Complete response rates, lesion area reduction, and disease control over 12 months were descriptively comparable. Importantly, the pilot design and absence of statistical powering preclude any conclusions regarding comparative efficacy, equivalence, or substitution potential. The extended follow-up period distinguishes our study from most AK trials, which typically assess outcomes after 3 months only, and offers additional insights into the durability of field-directed therapy [29]. The comparable clearance rates confirm that the novel formulation does not compromise imiquimod's immunomodulatory potential, which is primarily mediated through TLR7 activation.

Safety findings were consistent with the established profile of topical imiquimod. No treatment-related SAEs were observed in either arm. As this represented the first-in-human use of IMI.Gel, the absence of unexpected safety signals is reassuring but should be interpreted within the constraints of limited exposure. The most commonly reported local adverse events aligned with the known pharmacodynamic profile of topical imiquimod, primarily including erythema, scaling, and ulceration. Interestingly, patients receiving IMI.Gel more frequently required a second treatment cycle compared to Aldara. Given the exploratory nature of the dataset, no mechanistic or comparative conclusions can be drawn from this observation. Nonetheless, efficacy outcomes at long-term follow-up remained comparable between the groups.

QoL, assessed using the DLQI, improved over the course of treatment in both groups. However, baseline DLQI scores were already low, reflecting the perception of AK as a largely asymptomatic and minor condition, which is in line with prior study data [7, 30–33]. Future clinical trials should determine the appropriateness of the DLQI for this disease. At the same time, the low DLQI might yield relevant insights into this specific patient population. Many patients may underestimate the clinical relevance of AK due to the lack of symptoms and thus delay or entirely avoid treatment. Our cohort consisted of motivated patients who actively registered to participate in the study. Available literature data suggest that improved patient education and awareness are essential to enhance early diagnosis and therapeutic compliance in the broader AK population [8, 32, 34].

Nevertheless, several limitations of the study should be noted. Recruitment took place during the COVID-19 pandemic, leading to extended timelines and several patient withdrawals, potentially impacting statistical power. Moreover, the open-label design introduces the risk of observer and responder bias, particularly in subjective measures such as cosmetic outcome and patient satisfaction. The pilot scale, limited power, and exploratory analyses preclude definitive comparative conclusions. Larger, blinded, multicenter trials are required to validate safety, tolerability, and clinical performance and to formally assess comparative efficacy.

6 | Conclusion

In conclusion, IMI.Gel is a pharmaceutically optimized, well-tolerated, and cosmetically favorable alternative to Aldara for the treatment of AK. However, due to the exploratory pilot design of the present study, larger, randomized controlled trials are required to confirm these preliminary findings and to determine the comparative clinical performance of this formulation.

Author Contributions

Berenice M. Lang and Sophie Luise Meiser contributed equally to this work. Berenice M. Lang and Sophie Luise Meiser drafted the manuscript. Markus P. Radsak, Peter Langguth, and Petra Staubach conceived and developed the study concept. Isabella Hölzle, Jonas Pielenhofer, Berenice M. Lang, and Sophie Luise Meiser conducted the studies. Hilde Spahn-Langguth, Hansjörg Schild, Georg Hess, and Stephan Grabbe contributed to the study concept.

Acknowledgments

The authors would like to thank Dr. Pascale Anderle, HSeT Foundation, Switzerland, for her valuable advice and support in the statistical analysis of this study.

This work was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)—Project-ID 318346496-CRC1292 TP21N (Markus P. Radsak) TR156 TP A05 and KS01 (Markus P. Radsak and Hansjörg Schild), and CRC1066 TP B18 (Markus P. Radsak, Stephan Grabbe, and Peter Langguth) as well as the Federal Ministry of Education and Research grant FKZ 03THW13K04 (Markus P. Radsak).

Funding

This work was funded by the Deutsche Forschungsgemeinschaft, 318346496; Bundesministerium für Bildung und Forschung, FKZ 03THW13K04. Open-access funding was enabled and organized by Projekt DEAL.

Disclosure

Data are part of the results of the doctoral thesis of Jonas Pielenhofer [35] and Isabella Hölzle [36].

Conflicts of Interest

Berenice M. Lang has received honoraria and travel reimbursement from Galderma, Biofrontera, Almirall, Pierre Fabre, Pfizer, SUN Pharma, Novartis, and BMS. Stephan Grabbe has consulted for and received honoraria from BioNTech, BMS, Delcath Systems, Heraclin, MSD, Merck, Novartis, and Sun Pharma. Petra Staubach has received honoraria and travel reimbursement from AbbVie, Allergika, Amgen, Almirall, BioCryst, BMS, Celgene, CSL Behring, Boehringer Ingelheim, Janssen, Hexal, Leo Pharma, Eli Lilly, Novartis, Octapharma, Pfizer, Sanofi, Galderma, Pierre Fabre, Klinge-Pharma, Beiersdorf, L´Oreal, Incyte, KalVista, Celltrion, Takeda, Regeneron, UCB Pharma, and Stada Pharma. Markus P. Radsak has consulted for and received honoraria from AbbVie, Alexion, AOP, AstraZeneca, Beigene, BMS, Cogent, GSK, Johnson & Johnson, Lilly, MSD, Merck, Novartis, Otsuka, Pfizer, Roche, Ryvu Therapeutics, Sanofi-Aventis, and SOBI. The other authors declare no conflicts of interest.

Data Availability Statement

The patients source data used to support the findings of this study are available from the corresponding author upon request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Supporting Information.** Figure S1 Safety assessment was performed at each visit with highest values at Visit 4. Erythema was the most common reaction in both study groups. Figure S2 Percentage frequency of cosmetic outcome rating. Figure S3 Calculation of changes in skin quality assessment. Table S1 SAE listings.