ORIGINAL RESEARCH

Ingenol Mebutate 0.06% Gel for Field Treatment of Actinic Keratosis on 250 cm² of Skin on Trunk and Extremities: A Randomized Dose-Finding Trial

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ABSTRACT

Background: Field treatment of actinic keratosis (AK) can eradicate clinical and sub-clinical lesions; treatments for extended skin areas are required.

Methods: This randomized, double-blind, vehicle-controlled trial (NCT01998984) evaluated ingenol mebutate (IngMeb) 0.06% gel for AK treatment over extended areas. Adults with 5–20 AK lesions within a 250 cm² area of skin on the trunk (except chest) or extremities were randomized to: 2 days vehicle, 2 days IngMeb (2D, n=55); 1 day vehicle, 3 days IngMeb (3D, n=59); 4 days IngMeb (4D, n=49); or 4 days vehicle (n=61). Week 8 primary endpoint was complete clearance of AK lesions; secondary endpoints included reduction in AK count and partial clearance. Adverse events (AEs) were recorded and local skin responses (LSRs) assessed. A hierarchical testing scheme, starting with 3D versus vehicle, was used.

Results: In total, 224 patients were randomized. At Week 8, for 2D, 3D, 4D, and vehicle groups, complete clearance rates were 12.7%, 5.1%, 26.8%, and 0.0% (3D vs. vehicle, p=0.18); reductions in AK count were 63.0%, 66.8%, 73.6%, and 11.9%, respectively. LSR scores peaked at Day 5 (3D and 4D), and Days 5 and 10 (2D). Application-site pain and pruritus were common AEs. Of 15 neoplasm AEs, 14 were designated keratoacanthomas and one squamous cell carcinoma by central pathological review. The 4D group was closed based on pre-defined criteria.

Conclusions: All three regimens were effective at reducing AK count on trunk/extremities. The 4D treatment was not well tolerated. Complete clearance was not significantly different to vehicle.

INTRODUCTION

Actinic keratosis (AK) results from cumulative ultraviolet (UV) light exposure.[1] AK lesions present as hyperkeratotic papules and plaques often on an erythematous background;[2] they may progress to squamous cell carcinoma (SCC) if left untreated, and have a higher risk of progression the longer they are present.[3,4] Management of AK is typically achieved through lesion-directed or field-directed topical therapy.[3,5,6] Advanced imaging techniques show that areas of sun-exposed skin may contain both sub-clinical and clinically visible lesions, as well as areas of dysplastic cells in fields of cancerization.[6–8] Treating the entire field of sun-damaged skin, rather than only the clinically apparent lesions, is therefore ideal.

Ingenol mebutate (IngMeb) (Picato® LEO Pharma A/S Ballerup, Denmark) is indicated for the topical treatment of AK in areas of skin up to 25 cm^2. A short course of IngMeb gel (two or three consecutive days) was associated with a marked improvement in the clearance of AK on the face/scalp (IngMeb 0.015% gel) and trunk/extremities (IngMeb 0.05% gel) versus placebo.[9] The treatment effect was maintained long term.[10] Some patients, however, may require treatment over areas larger than 25 cm^2. A new-formulation gel containing a higher concentration of IngMeb, is being investigated for use over larger treatment areas. Previous investigations identified 0.06% as the maximum tolerated concentration for a 2-day (D) regimen applied to the full face, full balding scalp or approximately 250 cm^2 on the chest.[11] As a more aggressive regimen may be required for the treatment of the trunk and extremities, the current trial was designed to investigate the efficacy of extending the duration of IngMeb 0.06% gel treatment

(2-, 3- or 4D regimens), compared with vehicle, over 250 cm^2 of skin.

METHODS

Study Design

This was a phase II, randomized, multicenter (14 in the USA; 13 in Australia), double-blind, vehicle-controlled trial (NCT01998984). The protocol was approved by relevant review boards at each center. Informed written consent was obtained from all patients and the trial conducted according to the principles of the Declaration of Helsinki.

Patients (≥ 18 years) with 5–20 clinically typical, visible, discrete AK lesions within a contiguous area of approximately 250 cm^2 of skin on the trunk (except chest) or extremities were eligible for enrollment (supplementary materials provide exclusion criteria).

IngMeb 0.06% gel or vehicle gel was applied topically to a contiguous area of approximately 250 cm^2 on the trunk (except chest) or extremities, daily for four days. Patients were randomized 1:1:1:1 (stratified per trial site) to one of four treatment groups (Supplementary Figure 1): 2 days vehicle, 2 days IngMeb (2D); 1 day vehicle, 3 days IngMeb (3D); 4 days IngMeb (4D); 4 days vehicle (vehicle group). Treatment assignment was pre-planned and generated through an interactive web response system.

Outcomes

The primary endpoint was complete clearance of AK lesions (AKCLEAR 100) at Week 8. Secondary endpoints at Week 8 were reduction in AK count from baseline and partial clearance of AK lesions

(AKCLEAR 75), defined as ≥ 75% reduction from baseline in the number of clinically visible AK lesions. Dermatologic assessment of the treatment area was performed by a board-certified dermatologist or equivalent at baseline, and at Weeks 4 and 8. Where possible, the same dermatologist performed all examinations on an individual patient. Treatment areas were documented on a study transparency, using a 3-point landmark technique to locate and assess AK lesions during treatment. Photo-damage outcome assessments, comprising a visual and tactile evaluation by investigators of the change from baseline in the photo-damage of the patient's skin, were performed at Week 8.

Safety endpoints included the incidence and severity of local skin responses (LSRs) and adverse events (AEs), recorded at Days 1, 5, 10, 17, 31 and 56. LSRs were assessed quantitatively as described previously.[12] Patients completed a burning-sensation diary on all treatment days, recording onset, duration and feeling of burning (rated on a 5-point descriptive scale: no burning to unbearable burning). At Week 8, they completed a Treatment Satisfaction Questionnaire for Medication (TSQM) v1.4[13]. Cosmetic outcome was self-assessed using two questionnaires evaluating changes in overall appearance and feel of skin (rated on a 4-point scale: worsened, no change, somewhat improved, much improved).

Statistical Analysis

Sample size was determined based on the number of patients required to obtain 80% power when detecting a difference in AKCLEAR 100 rates between IngMeb and vehicle treatment groups, assuming a true estimate of 28% in the IngMeb groups and 7% in the vehicle group (significance level 0.05).

Efficacy analyses were performed on the full analysis set, defined as all randomized patients. A closed testing procedure was used to account for multiplicity. The 4D IngMeb treatment group was closed early on the recommendation of a data-monitoring committee (DMC) (see below) and patients were excluded from the final statistical model. Thereafter, the 3D IngMeb treatment group was to be tested first and, provided a significant result was observed, the 2D IngMeb arm was to be tested, thereby ensuring that the overall significance level did not exceed 5%.

The safety analysis set included all patients who received at least one application of trial medication and had safety information available post-treatment. Safety results were summarized using descriptive statistics. Two interim safety analyses (based on number of dose-limiting events) were conducted by a DMC when 12 and 23 patients, respectively, were randomized to each group and followed for 17 days. Primary and secondary endpoints were analyzed by a Cochran-Mantel-Haenszel test, adjusting for analysis site. Reduction in AK count from baseline to Week 8 was analyzed using a negative binomial regression (supplementary materials). STATA® version 13.2 was used for imputation of missing AK count. Statistical analyses were undertaken using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA) and the Medical Dictionary for Regulatory Activities version 15.1 used for coding of AEs and medical history.

RESULTS

Patients

In total, 266 patients enrolled in the study (03 February–22 August 2014) (Figure 1); 224 were randomized to treatment (42 screening failures), forming the full analysis and safety sets. Although the 4D group was closed early, data are presented

here because of the high number of patients completing treatment.

Regarding baseline demographics/disease characteristics, the median duration of AK in patients from Australia was more than twice that of patients from the USA (Table 1). Over 90% of patients had received previous treatment for AK. Treatment adherence was high; all four doses were received by 92.9% of patients.
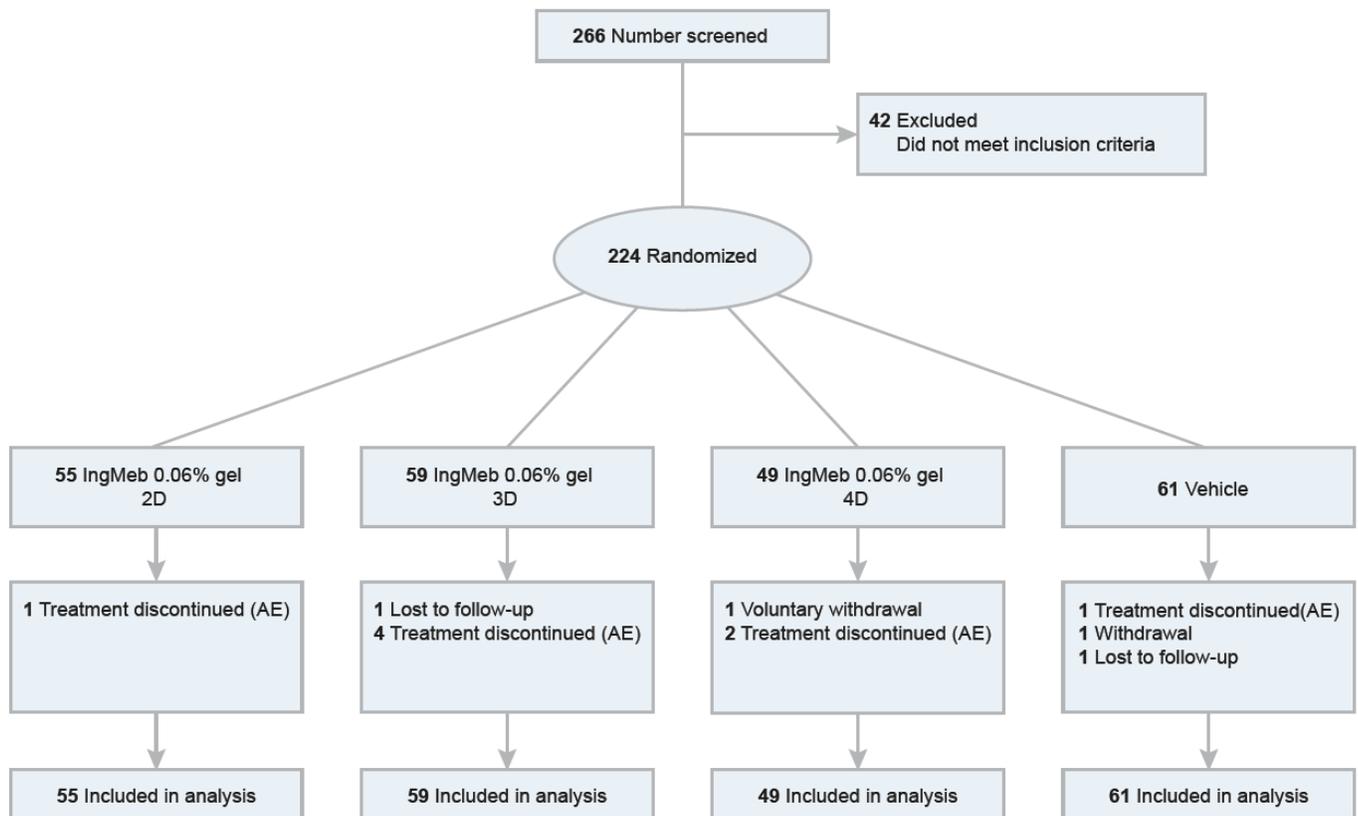
2D, 2-day group; 3D, 3-day group; 4D, 4-day group; AE, adverse event; IngMeb, ingenol mebutate.

Figure 1. Subject flow through the trial

Efficacy

At Week 8, AKCLEAR 100 was 12.7%, 5.1%, 26.8%, and 0.0% for 2D, 3D, 4D, and vehicle groups, respectively (Table 2). There was no difference in AKCLEAR 100 between the 3D and vehicle groups (p=0.18). The hierarchical analysis of the primary and secondary endpoints, and the absence of a statistically significant difference in the primary comparison (3D IngMeb vs. vehicle) meant statistical significance could not be claimed for the 2D versus vehicle comparison, or any secondary efficacy endpoints. However, values are included for information. Observed cases of AKCLEAR 100 varied by country and by baseline AK count. AKCLEAR 100 was higher in the USA than Australia and for patients with baseline AK counts of 5–9 lesions versus those with 10–20 lesions (Table 2).

Table 1. Baseline Demographics and Disease Characteristics

	Full Analysis Set (n=224)	USA (n=92)	Australia (n=132)
Sex, n (%)			
Male	144 (64.3)	62 (67.4)	82 (62.1)
Female	80 (35.7)	30 (32.6)	50 (37.9)
Age, years			
Mean (SD)	68.3 (10.5)	66.3 (10.4)	69.7 (10.3)
Race, n (%)			
White	224 (100.0)	92 (100.0)	132 (100.0)
Fitzpatrick skin type, n (%)			
I – Burns easily, never tans	77 (34.4)	12 (13.0)	65 (49.2)
II – Burns easily, tans minimally	122 (54.5)	64 (69.6)	58 (43.9)
III – Burns moderately, tans gradually (light brown)	22 (9.8)	13 (14.1)	9 (6.8)
IV – Burns minimally, always tans well (moderate brown)	3 (1.3)	3 (3.3)	0 (0.0)
Duration of AK, years			
Median (range)	12.0 (0–44)	8.0 (0–44)	17.0 (0–44)
Baseline AK count			
Median (range)	12 (5–20)	10 (5–20)	13 (6–20)

AK, actinic keratosis; SD, standard deviation.
n, number of patients.

Table 2. AKCLEAR 100 and reduction in AK count at Week 8

	AKCLEAR 100, n (%)				Reduction in AK count from baseline, % (SD)			
	IngMeb 0.06% gel			Vehicle	IngMeb 0.06% gel			Vehicle
	2D	3D	4D	(n=61)	2D	3D	4D	(n=61)
	(n=55)	(n=59)	(n=49)		(n=55)	(n=59)	(n=49)	
Overall [a,b,]	7.0 (12.7)[c]	3.0 (5.1)[c]	13.1 (26.8)[c]	0.0 (0)[c]	64.5[d,e]	68.3[d,e]	N/A	11.9[d,e]
P-value vs. vehicle	p=0.051[f,g]	p=0.18[f,g]	N/A	N/A	p<0.001[d]	p<0.001[d]	N/A	-
By baseline AK count[h]								
5–9	5/21 (23.8)	2/21 (9.5)	5/15 (33.3)	0/16 (0.0)	N/A	N/A	N/A	N/A
10–20	2/34 (5.9)	1/37 (2.7)	8/33 (24.2)	0/42 (0.0)	N/A	N/A	N/A	N/A
By country[h]								
USA	7/24 (29.2)	2/26 (7.7)	6/16 (37.5)	0/24 (0.0)	78.7 (26.4)	73.6 (23.5)	73.4 (32.6)	10.0 (20.5)
Australia	0/31 (0.0)	1/32 (3.1)	7/32 (21.9)	0/34 (0.0)	50.9 (33.3)	61.2 (32.1)	73.7 (24.4)	12.7 (27.2)

AK, actinic keratosis; CMH, Cochran–Mantel–Haenszel; IngMeb, ingenol mebutate; N/A, not available; SD, standard deviation.
n, number of patients.
AKCLEAR 100, complete clearance of AK lesions from baseline;
[a]Multiple imputation.
[b]Based on 1000 imputations of AK count at Week 8 using a negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset.
[c]n/1000 from 1000 imputations of AK count at Week 8 using a negative binomial regression model with factors treatment and analysis site and with log baseline AK count as offset.
[d]From negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset.
[e]Ratio of adjusted means (95% CI), p value: 2D vs. vehicle: 0.40 (0.32–0.51), p<0.001; 3D vs. vehicle: 0.36 (0.29–0.45), p<0.001; 3D vs. 2D: 0.89 (0.70–1.14), p=0.36.
[f]Adjusted for analysis site.
[g]CMH logit estimators were used for comparisons with vehicle due to absence of cleared patient in the vehicle group.
[h]Observed cases.

Treatment differences should be considered with caution due to the hierarchical procedure defined in the protocol. However, in the primary analysis using the multiple imputation method (supplementary materials), and excluding the 4D group, the adjusted percentage reduction in AK count from baseline was significantly greater than vehicle (11.9%) for IngMeb 2D (64.5%, p<0.001) and 3D (68.3%, p<0.001) groups (Table 2). For observed cases, the mean percentage reduction was numerically higher for the USA than Australia in the 2D (78.7% versus 50.9%, respectively) and 3D (73.6% versus 61.2%, respectively) groups, but similar within the vehicle (10.0% versus 12.7%) groups. Similarly, in the primary analysis, using the multiple imputation method and excluding the 4D group, AKCLEAR 75 was significantly greater than vehicle (2.0%) for IngMeb 2D (47.3%, p=0.002) and 3D (56.2%, p≤0.001) groups.

Safety

At baseline, the mean (standard deviation) composite LSR scores were 1.5 (1.1), 1.7 (1.2), 1.7 (1.2) and 1.7 (1.3) for the 2D, 3D, 4D and vehicle groups, respectively. Maximum mean composite LSR scores peaked at Day 5 in the 3D and 4D groups and at Days 5 and 10 in the 2D group. LSR scores in all IngMeb groups declined rapidly and were minimal four weeks after treatment (Figure 2).

The 4D group had the highest composite LSR score at Day 5 (11.8), followed by the 3D (8.8) and 2D (7.3) groups. The vehicle group had similar scores at all visits, corresponding to baseline scores for the IngMeb groups.

The majority of patients in the IngMeb groups experienced AEs of mild or moderate intensity. There were 12 AEs leading to treatment discontinuation in eight patients, including seven AEs of application site pain. AEs were considered to be treatment-related in most patients receiving IngMeb. The most common treatment-related AEs in the IngMeb groups were application-site pain (including burning sensation reported in the burning-sensation diary) (2D, 81.8%; 3D, 84.7%; 4D, 87.8%) and application-site pruritus (2D, 34.5%; 3D, 45.8%; 4D, 28.6%). Maximum burning sensation scores were reported at Days 1 and 2 in the 4D group and at Days 3 and 4 in both the 2D and 3D groups. Most patients in the vehicle group reported no burning sensation.

Sixteen AEs (most reported as SAEs) of 'neoplasms benign, malignant, and unspecified (including cysts and polyps)' were reported inside the treatment area in 12 patients (Australia, n=11; USA, n=1), distributed evenly across all IngMeb groups. Ten patients had a history of skin cancer. Fifteen AEs were reviewed by a central pathologist (consent to follow up was not obtained for one patient with one event of intraepidermal carcinoma) and 14 were diagnosed as keratoacanthoma (KA), all in patients from Australia. One was diagnosed as SCC (Supplementary Table 1). No other treatment-related SAEs were reported.

Other observations

Patient TSQM-derived scores for Satisfaction and Effectiveness were significantly greater in the 2D and 3D IngMeb groups than vehicle

(p<0.001; Supplementary Table 2). The majority (80–98%) of patients in the IngMeb groups were assessed by investigators as having improvements (minor, moderate or marked) in their global photo-damage from baseline to Week 8; 86% of patients in the vehicle group had no change (Figure 3A). There was a trend towards higher outcome scores with the 2D and 3D groups in the USA versus Australia; similar scores were observed in the 4D group (data not shown).

Across the IngMeb groups, improved changes in the overall appearance of the treatment area were reported by ≥ 80% of patients; improved changes in the overall feel of the treatment areas were reported by ≥ 70% of patients. Little difference in patient-reported cosmetic outcome between IngMeb groups was observed (Figure 3B). Around 10% of patients reported overall cosmetic improvements with vehicle.
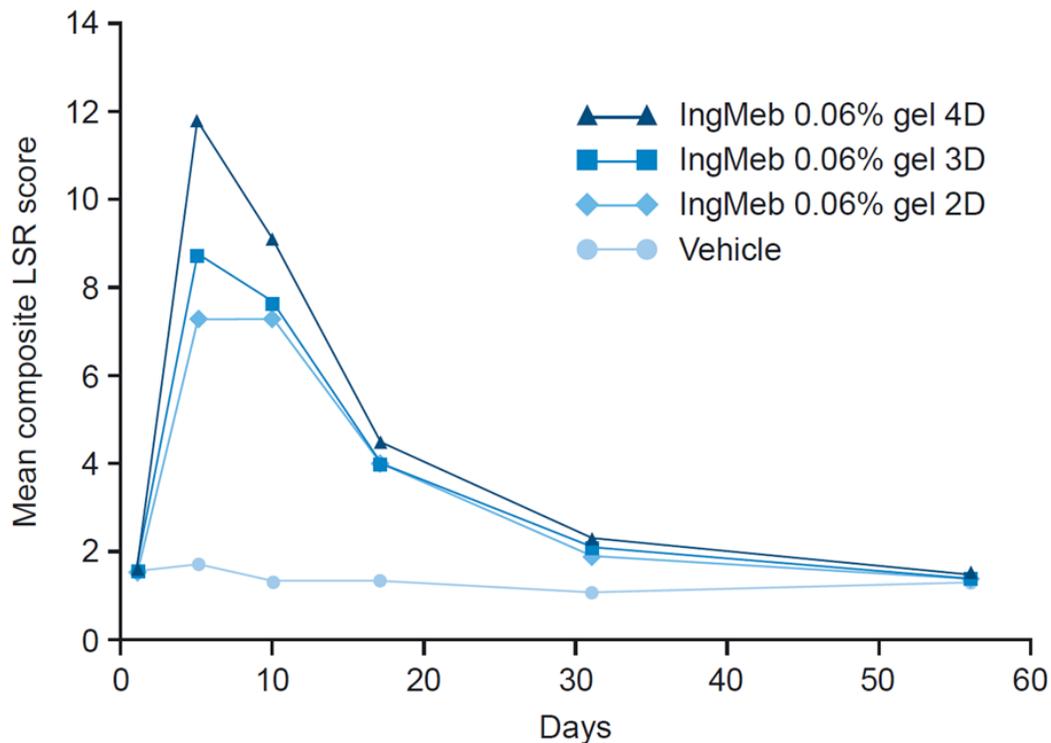
2D, 2-day group; 3D, 3-day group; 4D, 4-day group; IngMeb, ingenol mebutate; LSR, local skin responses.
Mean composite of LSR scores. A composite score was obtained by summing the 6 individual local skin responses (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration) scores at each visit.

Figure 2. Composite local skin responses over time
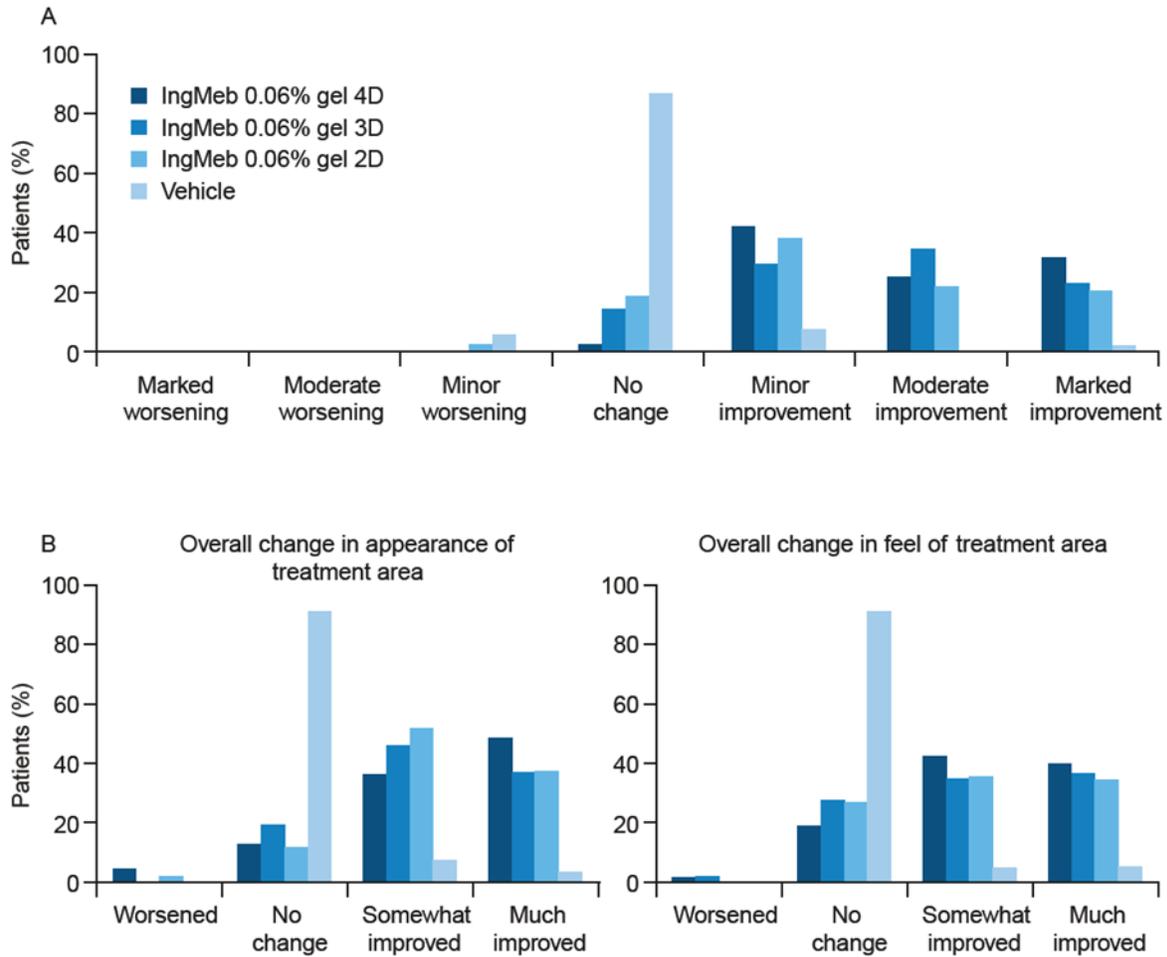
2D, 2-day group; 3D, 3-day group; 4D, 4-day group; IngMeb, ingenol mebutate.
A) Investigators' Global Photo-Damage Outcome at Week 8. The visual and tactile assessment of photo-damage change from baseline in the treatment area included an integrated assessment of fine wrinkling, coarse wrinkling, mottled pigmentation, roughness, sallowness, skin laxity and telangiectasia. The scoring was on a 7-point symmetric scale: marked improvement, moderate improvement, minor improvement, no change, minor worsening, moderate worsening and marked worsening. B) Patients' Cosmetic Outcome Assessment at End of Treatment.

Figure 3. Investigator and patient-reported cosmetic outcomes at Week 8

DISCUSSION

In this trial, a 3D application of IngMeb 0.06% gel to a treatment area of approximately 250 cm^2 on the trunk or extremities reduced AK count. However, a statistically significant difference in the primary endpoint of complete clearance (AKCLEAR 100) at Week 8 compared with vehicle was not observed (p=0.18).

Complete clearance rates observed in this trial were low overall, showed high variation, and a dependency on country and baseline AK count. When compared with IngMeb treatment of AK over a 25 cm^2 area,[9] lower complete clearance is to be expected because of the larger area and higher number of baseline lesions being treated. Of note, complete clearance in the 3D arm (5.1%) was low versus other treatment groups; however, a high number (48.3%) of patients in this group had one or two AK lesions remaining (Supplementary Figure 2). Complete clearance appeared to be higher for patients from the USA who generally had a shorter duration of AK and for those with fewer baseline AK lesions, suggesting that efficacy may be influenced by the extent of disease. One trial limitation was that no statistical claims can be made for the secondary endpoints, because of the pre-defined order of testing and lack of statistical significance for the primary endpoint. Numerical and clinically relevant effects were observed with 2D, 3D and 4D regimens versus vehicle for secondary endpoints (partial clearance: 47.3%, 56.2%, 60.4%, vs. 2.0%, respectively; mean reduction in AK count: 64.5%, 68.3%, 73.6%, vs. 11.9%, respectively). Similar partial clearance results have been observed in trials evaluating IngMeb on a treatment area of 25 cm^2: Lebwohl et al. reported partial clearance of 63.9% on the face/scalp and 49.1% on the trunk/extremities. They also reported a median percent reduction in lesion count of 83% and 75%, respectively, which was greater than vehicle (p<0.001).[9]

In this study, the 2D and 3D treatments were well tolerated; the 4D treatment was not. Based on the outcome of DMC interim safety analyses and pre-defined protocol criteria, the 4D treatment regimen was stopped prior to completing enrollment. Consistent with previous findings,[9] application-site AEs, including pain and pruritus, were the most frequent treatment-related events.

The use of non-standardized reporting of endpoints hinders cross-trial comparison with other currently available field-directed therapies, including 5-fluorouracil, imiquimod, diclofenac and photodynamic therapy.[5] Studies have generally focused on the face and scalp[14–17] rather than the extremities, where AK lesions are more difficult to treat and have shorter remission times.[10] Partial, but not complete, clearance results from the current trial, investigating treatment in the trunk and extremities, compare well with two previous studies with imiquimod 2.5% and 3.75% that investigated a scalp/facial treatment area > 25 cm^2.[18,19] In those studies, complete clearance rates were 30.6% and 35.6% for 2-week[18] and 25.0% and 34.0% for 3-week on/off/on treatment regimens.[19] Partial clearance rates were 48.1% and 59.4%[18] and 42.7% and 53.7%,[19] respectively.

Compliance is an issue with patient-administered treatment[5,9] and may explain why efficacy reported in clinical trials is not always reflected in the real-world. In a recent study, 88% of patients treated in a clinical setting were non-adherent with topical treatment; adherence fell, in line with increasing duration of treatment.[20] Shorter, simpler treatment regimens should improve adherence and outcomes.[21] In this trial, adherence with IngMeb was high, with 92.9% of patients receiving all four applications of treatment, confirming findings from previous IngMeb studies.[9]

Another advantage of short-course treatment is the predictable timing and relatively short duration of LSRs, which should improve patient satisfaction.[21] In the current study, LSR scores peaked at Day 5 in the 3D and 4D groups and at Days 5 and 10 in the 2D group; responses were minimal four weeks after treatment. These findings are similar to those reported over a 25 cm^2 treatment area – LSR score peaked at Day 4 for the face/scalp and at Days 3, 8 and 15 for the trunk/extremities.[9]

In this study, 14 of 15 neoplasms 'benign, malignant and unspecified' were designated KA by central pathology review, all in fair-skinned (type I) Australian patients. Although UV light is a major risk factor for development, KAs have been observed following a number of different skin therapies including imiquimod, chemical peel, and cryosurgery.[22–24] This treatment-associated development of KA may be due to inflammation-mediated mitogen-activated protein (MAP) kinase stimulation in the presence of UV-induced activating Ras mutations in keratinocytes in sun-damaged skin.[25] As the frequency of KA increases with increased sun exposure,[6,25] this may partially explain why KAs were observed exclusively in Australian patients.

Another contributing factor to the formation of KAs may be activation of nuclear factor kappa B (NF-κB), which is activated in both acute and chronic inflammation.[26] NF-κB is activated after imiquimod treatment[27] and treatment with IngMeb gel (LEO Pharma, unpublished data). NF-κB is a promoter of solid organ tumors,[28] and hyperactivation of NF-κB in skin may lead to KA formation.[29] This may also explain why primarily KAs, but not SCCs, are seen after IngMeb treatment, as there is accumulating evidence from mouse studies that NF-κB inhibition, rather than activation, induces epidermal hyperplasia and promotes development of cutaneous SCC.[30–33]

The impact of AK on an individual's physical and emotional well-being should be considered in clinical management. AK may be associated with pain, sensitivity to touch, bleeding, concern about appearance (e.g. embarrassment about scarring), and can negatively impact health-related quality of life.[34–37] In this study, ≥ 70% of patients reported improved cosmetic outcomes with IngMeb, with improved appearance and feel of the treated area.

CONCLUSIONS

The reduction in AK count from baseline and the partial clearance results, along with the predictable LSR profile, support the efficacy of IngMeb 0.06% gel optimized for larger treatment areas of approximately 250 cm^2 on the trunk and extremities, when applied for 2 or 3 consecutive days.

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