

Maximum tolerated dose of PEP005 Topical Gel for the treatment of actinic keratosis

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Abstract

This phase IIa, open-label, dose-escalation, cohort study determined the maximum tolerated dose (MTD) of PEP005 (ingenol-3-angelate) Topical Gel when applied to an area of skin affected by actinic keratosis (AK). Twenty-two subjects, each with one AK lesion in an area of skin on the shoulders, chest, back or arms were treated on day 1 and day 2 with PEP005 Topical Gel at a concentration of 0.01%, 0.025%, 0.05% or 0.075% PEP005. The study demonstrated an MTD of 0.05% PEP005 Topical Gel administered once daily for two consecutive days to an area of skin affected by AK. All treated subjects completed the trial and the incidence of adverse events (AEs) was low. The most common treatment-emergent AEs were mild or moderate in intensity. Subjects were evaluated at all study visits for Local Skin Responses (LSRs), the most frequent of which were erythema, flaking/scaling/dryness and scabbing/crusting. Two subjects in the 0.075% PEP005 Topical Gel cohort experienced dose-limiting toxicities (DLTs) of severe scabbing/crusting and severe flaking/scaling/dryness. Pharmacokinetic analysis of two subjects in the 0.05% PEP005 Topical Gel cohort determined that whole blood concentrations of PEP005 were below quantifiable limits, indicating that there was no detectable systemic absorption of PEP005 following application of 0.05% PEP005 Topical Gel. At the end-of-study assessment (day 29), complete clinical clearance was reported in six subjects (60.0%) and marked clinical clearance in two subjects (20%) in the 0.05% PEP005 Topical Gel cohort. This study showed that the MTD of 0.05% PEP005 Topical Gel administered once daily for two consecutive days is a safe and effective treatment for clearance of AK lesions.

Introduction

AK is a precancerous skin lesion that, left untreated, can progress into squamous cell carcinoma. The prevalence of AK in the USA was estimated at 58 million in 2004 and the associated annual direct costs of treating AK were estimated at US\$1.2 billion.¹

Current treatments for AK include cryotherapy, surgery, photodynamic therapy and topical pharmacotherapy with 5-fluorouracil, diclofenac or imiquimod.² However, these treatments can have poor cosmetic outcomes, including scarring and skin pigmentation changes. The existing pharmacotherapies also generally require a long duration of treatment.

The compound PEP005 (ingenol-3-angelate) was isolated from the sap of *Euphorbia peplus*, a plant used for centuries for the treatment of various skin conditions. PEP005 has a two-fold mechanism of action: local primary necrosis and induction of a neutrophil-mediated immune response.^{3,4} In a previous phase IIa clinical trial, PEP005 Topical Gel at a concentration of 0.05% cleared 71% of AK lesions treated and was generally well tolerated.⁵ However, the optimal dose level and treatment regimen have yet to be determined.

This phase IIa, dose-escalation cohort study (protocol PEP005-004) investigated the MTD of PEP005 Topical Gel when applied to an area of skin containing a target AK lesion. Secondary objectives included the evaluation of clinical efficacy and systemic absorption of the drug.

Methods

This open-label, dose-escalation cohort study enrolled patients with AK who received two consecutive daily applications of PEP005 Topical Gel at concentrations from 0.01%. Eligible patients were aged ≥ 18 years and had one AK lesion with a diameter of 3–15 mm on the shoulders, chest, back or arms selected for treatment. PEP005 Topical Gel (90 μ L) was applied once daily on two consecutive days over a 3 cm \times 3 cm area of skin containing the target lesion. The planned dose levels were 0.01%, 0.025%, 0.05%, 0.075% and 0.1%. Three patients were initially entered at the lowest dose level, with an additional three patients being entered in the event of a DLT; DLT was defined as a severe LSR observed by the investigator prior to treatment on day 2 or on day 8. The MTD was defined as one dose level below the dose that produced DLTs in at least two of six patients. Once the MTD was defined, 10 patients were treated at that dose level to characterize the safety profile and systemic absorption of PEP005 Topical Gel. The following LSRs were recorded at each study visit: edema, erosion/ulceration, erythema, flaking/scaling/dryness, hyperpigmentation, hypopigmentation, scabbing/ crusting, vesicles, and weeping/exudates.

Hematologic, biochemical and urinalysis parameters were assessed at baseline, and on days 8 and 29 (end of study). AEs were assessed at each visit, and clinical response was measured on days 2, 8, 15 and 29.

Clinical response to treatment was determined by comparing an assessment of the lesion with an assessment on day 1. A six-point scale was used to evaluate response: complete clearance (100% improvement, no evidence of residual disease), marked clearance (50–90%, significant improvement with some residual disease), slight clearance (10–50%), unchanged ($\pm 10\%$), worsened (clinically observable growth), or unable to be assessed.

Results

Patient characteristics and treatment

A total of 22 patients were enrolled at a single center in the USA (Table 1). All patients had at least one comorbidity, including cardiovascular (77.3%), musculoskeletal (59.1%), genitourinary (45.5%), gastrointestinal (40.9%), and endocrine (27.3%) disorders. In addition, 95.5% of patients had a skin condition other than AK at baseline. All patients completed the planned course of therapy with PEP005 Topical Gel.

Table 1. Patient characteristics at baseline

Characteristics (n = 22)		Fitzpatrick–Pathak skin type* (n = 22)	
Mean age in years (range)	73.4 (64–87)	Type I	4 (18.2%)
No. of males (%)	16 (72.7%)	Type II	6 (27.3%)
No. of Caucasians (%)	22 (100%)	Type III	10 (45.5%)
		Type IV	2 (9.1%)
Duration of AK (months)		Prior AK treatments	
Mean	76.9	Cryotherapy/liquid nitrogen	21 (95.5%)
Range	0–248	5-fluorouracil	8 (36.4%)

* Fitzpatrick–Pathak skin types: I = burns easily, rarely tans; II = burns easily, tans minimally; III = burns moderately, tans gradually; IV = burns minimally, tans well; V = rarely burns, tans profusely; VI = never burns, deeply pigmented.

Local Skin Responses

LSRs were mostly mild or moderate in intensity, with moderate and severe reactions occurring predominantly at the 0.05% and 0.075% concentrations. These reactions were as expected and were predictable by the mechanism of action of PEP005. Table 2 summarizes LSRs in the 0.05% cohort. Most LSRs were tumor-specific, with approximately 17% of reactions having perilesional involvement. The duration of LSRs ranged from 6 to 43 days and most had resolved by day 29 (end of study).

Erythema and flaking/scaling/dryness were the most common LSRs. However, most patients had mild flaking/scaling/dryness (21 patients) and mild erythema (19) prior to treatment. Moderate LSRs were most commonly observed on day 8. The moderate LSRs recorded on day 8 in the 0.05% PEP005 Topical Gel cohort were flaking/scaling/dryness (7 patients; 70%), erythema (5; 50%), scabbing/crusting (5; 50%), edema (1; 10%), and erosion/ulceration (1; 10%). Severe LSRs occurred in a total of three patients (see *Maximum tolerated dose*). A typical series of LSRs resulting from two applications of PEP005 Topical Gel 0.05% is shown in Figure 1.

Table 2. Local Skin Responses in patients treated with PEP005 Topical Gel 0.05% (n = 10)

	Intensity of LSR by study day (patients)*		
	Mild	Moderate	Severe
Day 1 (predose)	9 (90%)	1 (10%)	0
Day 1 (postdose)	9 (90%)	1 (10%)	0
Day 2	9 (90%)	4 (40%)	0
Day 8	8 (80%)	8 (80%)	0
Day 15	10 (100%)	2 (20%)	1 (10%)
Day 29 (end of study)	10 (100%)	0	0

LSR, Local Skin Response; * Patients could have more than one response at each timepoint.

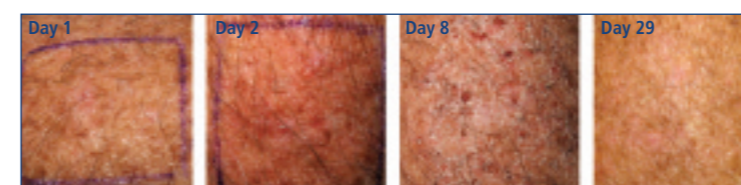


Figure 1. Local Skin Response on days 1, 2, 8 and 29 (end of study) in a representative patient treated with PEP005 Topical Gel 0.05%.

Other adverse events

Overall, the incidence of AEs was low and no serious treatment-related AEs were observed (Table 3). The most common treatment-emergent AEs were application-site reactions, which were documented for one patient (33.3%) treated with 0.01% PEP005 Topical Gel, six patients (60%) treated with 0.05% gel and five patients (83.3%) treated with 0.075% gel. Application-site reactions that occurred in more than one patient were pruritus (11 patients), irritation (6) and pain (3). Other AEs were not treatment-related and included one case each of herpes zoster infection, urinary tract infection, joint swelling, cough and xeroderma. The one serious AE was a case of aortic valve disease considered unrelated to treatment with PEP005 Topical Gel. No patients discontinued treatment due to AEs.

Maximum tolerated dose

DLTs occurred in two patients in the 0.075% cohort: severe scabbing/crusting and severe flaking/scaling/dryness were observed in one patient, and the other experienced severe scabbing/crusting. Only one severe LSR was documented in the 0.05% cohort (flaking/scaling/ dryness). All LSRs had resolved or returned to mild by day 29 (end of study). The MTD of PEP005 Topical Gel for the field treatment of AK was established as 0.05%.

References: 1. The Lewin Group; Society for Investigative Dermatology; American Academy of Dermatology Association. *The Burden of Skin Diseases 2005*. Cleveland/Washington DC: SID/AADA, 2005. 2. Balkrishnan R, Cayce KA, Kulkarni AS et al. *J Dermatolog Treat* 2006; 17: 162–6. 3. Ogbourne SM, Suhrbier A, Jones B et al. *Cancer Res* 2004; 64: 2833–9. 4. Challacombe JM, Suhrbier A, Parsons PG et al. *J Immunol* 2006; 177: 8123–32. 5. Siller G et al. Ingenol-3-angelate (PEP005) gel, a novel treatment for actinic keratoses: results of a randomised double-blind placebo-controlled multicentre safety and efficacy study. Manuscript in preparation.

Images have been digitally color-balanced, cropped and resized (to account for minor differences in camera positioning), but are otherwise unaltered. This study was funded by Peplin.

Table 3. Incidence of treatment-emergent adverse events (excluding Local Skin Responses)

Adverse events	PEP005 Topical Gel			
	0.01% (n = 3)	0.025% (n = 3)	0.05% (n = 10)	0.075% (n = 6)
Patients with AEs				
At least one AE	2 (66.7%)	1 (33.3%)	8 (80%)	5 (83.3%)
Any serious AEs	0	0	1 (10%)	0
Any severe AEs	0	0	1 (10%)	0
AEs deemed drug-related*	1 (33.3%)	0	6 (60%)	5 (83.3%)
Summary of AEs				
Total number of AEs [†]	5	1	19	12
Mild	5 (100%)	1 (100%)	16 (84.2%)	12 (100%)
Moderate	0	0	2 (10.5%)	0
Severe	0	0	1 (5.3%)	0
AEs deemed drug-related*	2 (40%)	0	13 (68.4%)	9 (75%)

AEs, adverse events; * AEs with an unknown, possible, probable or definite relationship to the study drug; [†] includes events reported more than once by the same patient.

Lesion clearance

At the end-of-study assessment, complete lesion clearance at the MTD (0.05%) was documented in six patients (60%) and marked lesion clearance in two patients (20%). Four patients treated with PEP005 Topical Gel 0.05% or 0.075% had an unscheduled follow-up 12–15 days after the end of study. All of these patients showed further improvement in clinical response. Overall, the complete response rate in the MTD cohort was 70% (Figures 2 and 3).

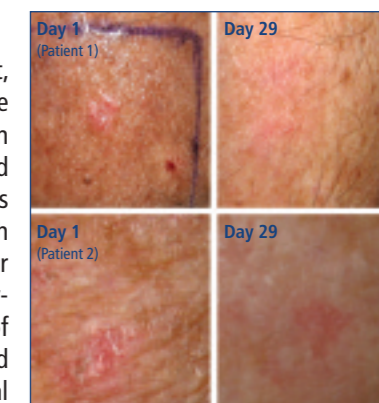


Figure 2. Complete clearance of AK lesion after treatment with PEP005 Topical Gel 0.05%. Representative photographs are shown for two patients on day 1 and day 29 (end of study).

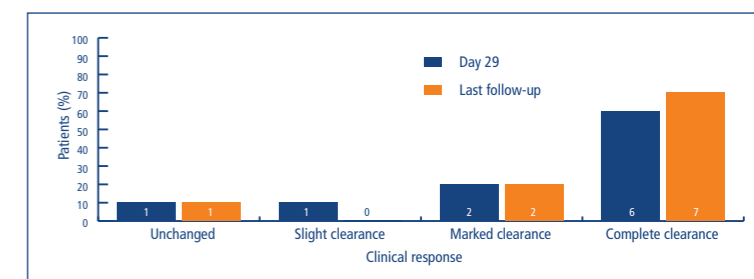


Figure 3. Clearance of AK lesions in patients treated with PEP005 Topical Gel 0.05% (n = 10). The last follow-up was day 29 (end of study) in nine patients and day 44 in one patient.

Pharmacokinetics

Blood samples for pharmacokinetic analysis were obtained from two patients in the 0.05% cohort. Whole-blood concentrations of PEP005 and its major metabolites were below quantifiable limits (< 0.01 ng/mL), indicating no detectable systemic absorption of PEP005 Topical Gel.

Discussion and conclusions

PEP005 Topical Gel at a concentration of 0.05% has a favorable tolerability profile and shows promising efficacy when applied to an area of skin containing an AK lesion. While this was primarily a safety study designed to establish the MTD, 70% of patients in the 0.05% cohort experienced complete clearance of target AK lesions, which is consistent with results from a previously completed phase IIa study in AK (PEP005-001 study).⁵ The MTD of 0.05% is the recommended dose for future clinical trials of PEP005 Topical Gel for the field treatment of AK.