

Safety and efficacy of PEP005 Topical Gel for the treatment of nodular and superficial forms of basal cell carcinoma

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Abstract

Topical therapies have been shown to be efficacious in the treatment of nonmelanoma skin cancer (NMSC). A new chemical entity, PEP005 (ingenol-3-angelate), identified and purified in Australia from the plant species *Euphorbia peplus*, is now being investigated for the treatment of some NMSC. We report here the results of safety and efficacy studies of the application of PEP005 in a gel formulation in the treatment of superficial basal cell carcinoma (sBCC) and nodular basal cell carcinoma (nBCC). Two phase IIa, multicenter, double-blind, randomized, vehicle-controlled, parallel-group studies investigated the safety and efficacy of PEP005 Topical Gel when applied to biopsy-proven nBCC or sBCC. Fifty-eight and 60 subjects each with one nBCC or sBCC lesion, respectively were randomized into one of two treatment arms: day 1 and day 2, or day 1 and day 8. Subjects in each treatment arm were treated with 0.0025%, 0.01%, 0.05% PEP005 Topical Gel or vehicle. The results in both trials demonstrated a favorable safety profile with a low incidence of adverse events (AEs). Most treatment-emergent AEs were classified as mild or moderate. Only one subject treated with 0.05% PEP005 Topical Gel on day 1 and day 2 (sBCC) had a severe AE. The severe AE, skin exfoliation, occurred outside the treatment area and was considered 'probably related to treatment'. Subjects were evaluated at all study visits for Local Skin Responses (LSRs), the most frequent of which were erythema and flaking/scaling/dryness. The majority of LSRs were reported as mild or moderate and had resolved within 1 month of completion of treatment. There was a dose response with higher concentrations resulting in more prevalent and increased severity of LSRs. There was no statistical difference in terms of safety or efficacy between treatment arms in either study. There was a dose-response relationship between concentration and clinical clearance, with 0.05% PEP005 Topical Gel being the most effective in both studies. At the 0.05% concentration, with two consecutive daily treatments on a per lesion basis for sBCC, there was a 71% histological clearance rate versus 0% for vehicle ($p = 0.02$). At the 0.05% concentration, with two daily treatments on a per lesion basis for nBCC, there was a 25% histological clearance rate, which was not statistically significant versus vehicle. These studies showed that 2 days of application of PEP005 Topical Gel appears to have a favorable safety profile in the treatment of both nBCC and sBCC. Furthermore, 2 days' application of PEP005 Topical Gel appears to have a favorable efficacy profile for sBCC. These data provide the basis to further develop the safety and efficacy of PEP005 Topical Gel for the treatment of both sBCC and nBCC.

Introduction

NMSCs, including BCC, are the most commonly diagnosed cancers.^{1,2} BCC is most often treated with surgery. Nonsurgical treatments include radiation therapy, photodynamic therapy, topical imiquimod or 5-fluorouracil.^{2,3} While acceptable cure rates can be obtained with surgery, patients are often left with scars and some are poor candidates for surgery for medical or psychosocial reasons. Over the past decade, pharmaceutical therapies have demonstrated clinically significant clearance rates for NMSC with minimal scarring. However, they can have prolonged and arduous courses of therapy, can be painful and can result in significant and prolonged side effects.³ It is not uncommon for full treatment courses to not be followed as a result of painful or unsightly side effects, thereby limiting the activities of these drugs. Because of this, alternative treatments for BCC are being investigated.

The sap of *Euphorbia peplus* (petty spurge) has been used for centuries as a treatment for skin conditions including cancers of the skin. Documentation of its use by medical professionals to treat BCC dates from the early 20th century.⁴ A case of biopsy-proven cure of a BCC following the application of the sap has also been reported.⁵ Analysis of the sap of *E. peplus* led to the identification of ingenol-3-angelate (I3A), or PEP005 as it is now known, as the active principle.⁶ A commercial purification process has been developed to extract I3A from *E. peplus*, enabling PEP005 to be produced in commercial quantities according to Good Manufacturing Practice.

Preclinical studies indicate that PEP005 has a novel mechanism of action that incorporates two distinct and complementary activities. PEP005 is highly hydrophobic and as such, remains localized to the site of administration and is not systemically absorbed. Within hours of application, PEP005 directly induces cell death by primary necrosis.⁶ As a consequence and via the ability of PEP005 to activate protein kinase C and pro-inflammatory cytokines,⁷ PEP005 also induces an inflammatory response at the site of application. This inflammatory response, which is clinically observed within 24–48 hours of application, is characterized

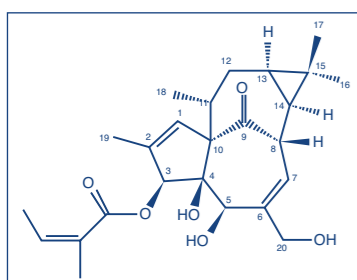


Figure 1. Chemical structure of PEP005.

by a massive infiltration of neutrophils.⁸ Treatment with PEP005 also results in the generation of tumor-specific antibodies, ultimately leading to neutrophil-mediated, antibody-dependent cellular cytotoxicity.⁸ In combination, these mechanisms of action give PEP005 a highly localized, rapid and specific anti-cancer activity.^{6,8}

The safety and efficacy of two applications of PEP005 as a treatment for nBCC or sBCC has been evaluated in two separate phase IIa clinical trials that used essentially identical methodology.

Methods

Studies PEP005-002 (nBCC) and PEP005-003 (sBCC) were both phase IIa, multicenter, double-blind, randomized, placebo-controlled, parallel-group studies. The primary objective was to evaluate the safety of PEP005 Topical Gel at three concentrations, 0.0025%, 0.01% and 0.05%, administered according to one of two schedules: day 1 and day 2, or day 1 and day 8. There was a final assessment of lesions on day 85 (end of study) in both studies. Secondary objectives were to evaluate the efficacy of PEP005 Topical Gel, to determine a recommended treatment regimen, and to evaluate patients for cosmetic outcome. Safety was assessed in the intent-to-treat population. Clinical efficacy was determined in the as-treated population by assessing the extent of BCC lesion clearance at each study visit relative to baseline. This was evaluated as: complete clearance (no evidence of residual disease), marked clearance (50–90% improvement), slight clearance (10–50% improvement), unchanged ($\pm 10\%$), or worsened (clinically observable growth). Histological efficacy was determined at the end of study by excision of the treated lesion.

Male or female (not of childbearing potential) patients aged ≥ 18 years who had one biopsy-proven BCC lesion on the arm, shoulder, chest, face, neck, abdomen, back, leg or scalp were enrolled. PEP005 Topical Gel was applied to a circular area containing the selected lesion. Both the volume of gel applied (70 or 100 μL ; $\sim 0.1 \mu\text{L}/\text{mm}^2$) and the circular area were proportionate to the longest lesion diameter.

Results

Fifty-eight patients with nBCC and 60 patients with sBCC were enrolled and randomized into each separate study. The study population was 100% Caucasian and predominantly male, with an age range of 34–87 years. Two patients in both the nBCC (3.4%) and sBCC (3.3%) studies received only one application of study medication as a result of a severe LSR on the scheduled second day of treatment. One patient withdrew from the nBCC study due to progression of a neoplasm distant to the treatment area that required clinical intervention prior to completion of the study. There were no statistically significant differences in safety or efficacy between the two treatment schedules in either study. Data from the two arms were therefore combined for subsequent analyses. Application of 0.05% PEP005 Topical Gel to nBCC lesions resulted in complete histological clearance and

complete or marked clinical clearance of 25% and 37.5% of lesions, respectively. In patients with sBCC, application of 0.05% Topical Gel for two consecutive days resulted in a 71% histological clearance rate ($p = 0.02$ versus vehicle) and an 86% complete or marked clinical clearance rate. In both studies, the most effective concentration of PEP005 Topical Gel on all measures of efficacy was the highest concentration tested, 0.05%.

No drug-related serious AEs were reported in either study. One patient with sBCC treated with 0.05% PEP005 Topical Gel developed severe localized skin exfoliation; this occurred outside the treatment area and was considered 'probably related to treatment'. This patient completed the study with no long-term sequelae. In both studies, PEP005 Topical Gel was well tolerated with a favorable safety profile (Tables 1 and 2). The most frequently reported LSRs were erythema, scabbing/crusting, and flaking/scaling/dryness. Most LSRs were mild or moderate and typically resolved within 4 weeks. All LSRs were as expected and predictable.

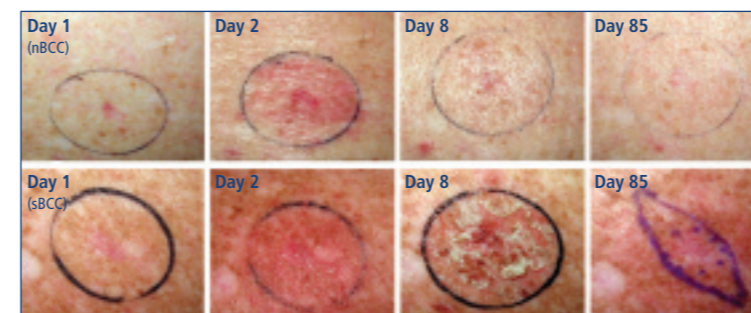


Figure 2. Effect of treatment with PEP005 Topical Gel on nBCC (PEP005-002) or sBCC (PEP005-003). Each series represents a single lesion from a single patient.

Table 1. Most intense Local Skin Responses in patients with nBCC (PEP005-002)

Local Skin Response	PEP005 Topical Gel (moderate; severe)			
	Vehicle gel (n = 12)	0.0025% (n = 14)	0.01% (n = 16)	0.05% (n = 16)
Itch	–	7%; 0%	6%; 0%	31%; 0%
Erythema	–	7%; 0%	38%; 0%	50%; 19%
Edema	–	–	13%; 6%	31%; 0%
Erosion/ulceration	–	7%; 0%	–	19%; 6%
Scabbing/crusting	8%; 0%	7%; 0%	13%; 0%	31%; 0%
Weeping/exudates	8%; 0%	7%; 0%	–	13%; 0%
Vesicles	8%; 0%	–	6%; 13%	13%; 25%
Flaking/scaling/dryness	–	–	19%; 0%	38%; 6%
Hypopigmentation	–	–	–	–
Hyperpigmentation	–	–	6%; 0%	–

References: 1. Marks R. *J Dermatol* 1995; 22: 853–7. 2. Bath-Hextall F, Bong J, Perkins W, Williams H. *BMJ* 2004; 329: 705. 3. Rosen RH. *Med Today* 2006; 7: 25–37. 4. Maiden JH. *Ag Gazette NSW* 1917; 28: 131–2. 5. Weedon D, Chick J. *Med J Aust* 1976; 1: 928. 6. Ogbourne SM, Suhrbier A, Jones B et al. *Cancer Res* 2004; 64: 2833–9. 7. Kedeei N, Lundberg DJ, Toth A, Welburn P, Garfield SH, Blumberg PM. *Cancer Res* 2004; 64: 3243–55. 8. Challacombe JM, Suhrbier A, Parsons PG et al. *J Immunol* 2006; 177: 8123–32.

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 2. Most intense Local Skin Responses in patients with sBCC (PEP005-003)

Local Skin Response	PEP005 Topical Gel (moderate; severe)			
	Vehicle gel (n = 12)	0.0025% (n = 16)	0.01% (n = 16)	0.05% (n = 16)
Itch	8%; 0%	–	6%; 0%	19%; 0%
Erythema	–	19%; 0%	25%; 6%	63%; 0%
Edema	–	–	0%; 6%	13%; 0%
Erosion/ulceration	–	–	6%; 0%	6%; 6%
Scabbing/crusting	–	6%; 0%	38%; 0%	50%; 6%
Weeping/exudates	–	–	–	6%; 0%
Vesicles	–	–	6%; 13%	6%; 13%
Flaking/scaling/dryness	–	–	31%; 0%	25%; 13%
Hypopigmentation	–	–	–	13%; 0%
Hyperpigmentation	–	–	–	–

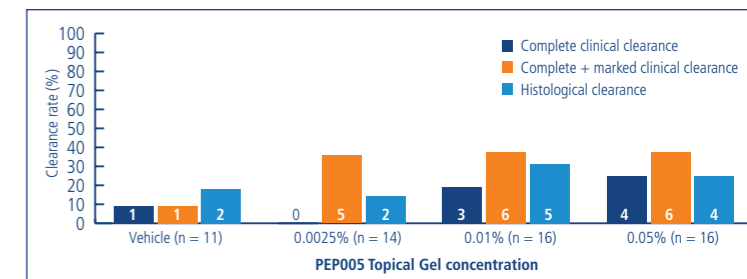


Figure 3. Effect of PEP005 on clearance of nBCC lesions (PEP005-002).

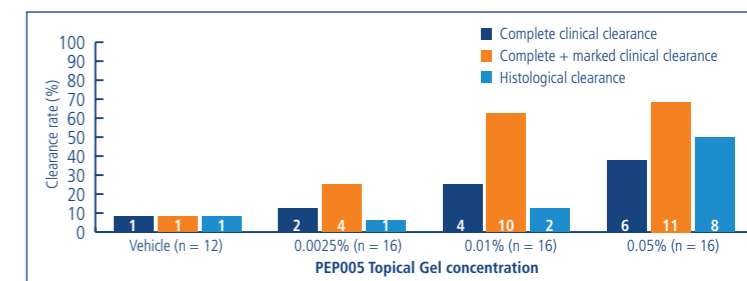


Figure 4. Effect of PEP005 on clearance of sBCC lesions (PEP005-003).

Discussion and conclusions

These findings indicate that PEP005 Topical Gel at doses of 0.0025%, 0.01%, and 0.05% is safe and well tolerated in patients with sBCC or nBCC. There were no drug-related systemic AEs, no evidence of long-term scarring and the cosmetic outcome at the site of treatment was excellent. The most efficacious dosage used in this study was 0.05% PEP005 Topical Gel, with two consecutive daily doses resulting in complete histological clearance of 71% of sBCC lesions. The higher clearance rate in sBCC compared to nBCC was expected given the thicker and deeper structure of nBCC lesions. While the efficacy of PEP005 Topical Gel was statistically significant only for sBCC, both studies showed a clear clinical dose response (Figures 3 and 4), indicating that increasing the concentration of study drug would most likely lead to improved efficacy. The frequency and severity of LSRs also increased with dose, consistent with the predictable clinical outcomes of PEP005's mechanism of action.

Pharmaceutical therapies have become common tools for the treatment of NMSC in the last decade. More advanced therapies that have improved efficacy, shorter treatment regimens with less severe and prolonged side effects, and which produce excellent cosmetic outcomes, are now required. PEP005 Topical Gel, a novel, naturally derived, pharmaceutical product discovered in Australia, proved to be safe and well tolerated at the doses and regimens used in these studies. PEP005 Topical Gel has a short course of therapy, is fast acting and shows encouraging signs of efficacy in BCC. Subsequent clinical trials will evaluate higher doses of PEP005 Topical Gel administered on two consecutive days to patients with sBCC.