## 2 SYNOPSIS

<table>
<thead>
<tr>
<th>Name of company:</th>
<th>Peplin Operations Pty Ltd</th>
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<tbody>
<tr>
<td>Name of finished product:</td>
<td>PEP005 Topical Gel</td>
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<tr>
<td>Name of active ingredient:</td>
<td>3-angeloyl ingenol</td>
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</tbody>
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**Title of Study:** A multi-center, randomized, double-blind, parallel-group, vehicle-controlled study to determine the safety of PEP005 0.0025%, 0.01%, and 0.05% gel with two treatment schedules, Day 1 and Day 2 or Day 1 and Day 8 applications to actinic keratoses

**Investigators:**
- Prof [Redacted]
- Dr [Redacted]
- Dr [Redacted]
- Dr [Redacted]

**Study Centers:**
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

**Study Period:**
- First patient entered: 17 March 2005
- Last patient completed: 14 October 2005

**Clinical Phase:** Phase IIa

**Publications:** None

**Objectives:**
- **Primary Objective:** To determine the safety of PEP005 Topical Gel at 0.0025%, 0.01%, and 0.05% administered as two applications to patients with actinic keratosis (AKs) on the arms, shoulders, chest, face, and/or scalp under the following two treatment schedules: Day 1 and Day 2 or Day 1 and Day 8.

- **Secondary Objectives:**
  - To evaluate the efficacy of PEP005 0.0025%, 0.01% and 0.05% Topical Gel administered under the following two treatment schedules: Day 1 and Day 2 or Day 1 and Day 8
  - To determine a recommended treatment regimen for AK
  - To evaluate patients for cosmetic outcome

**Methodology:** This was a multi-center, double-blind, randomized, vehicle-controlled, parallel-group comparison of two treatment schedules, Day 1 and Day 2 (Treatment Arm A) or Day 1 and Day 8 (Treatment Arm B) of three concentrations (0.0025%, 0.01%, and 0.05%) of PEP005 Topical Gel in patients with at least five AK lesions located on the arms, shoulders, chest, face, and/or scalp. All patients were required to have confirmed AK by punch biopsy of one representative lesion prior to study entry. Punch biopsy specimens were read by a central reviewer. Patients were screened for study entry, and after randomization to Treatment Arm A or B, were assessed for safety and efficacy at visits occurring on Days 2, 8, 15, 29, 57, and 85 following the last day of study drug application. Additional, post-Day 85 safety visits were allowed to confirm adequate healing of the punch biopsy areas or resolution of any ongoing local skin adverse events (AEs).
Name of company: Peplin Operations Pty Ltd
Name of finished product: PEP005 Topical Gel
Name of active ingredient: 3-angeloyl ingenol

Number of Patients: The number of patients planned was approximately 60. A total of 72 patients were screened, 63 were randomized and analyzed for efficacy, and 58 were analyzed for safety.

Diagnosis and Main Criteria for Inclusion: Adults with at least five individual AK lesions on the arm, shoulders, chest, face, and/or scalp.

Dosage, Administration, and Duration of Treatment:
Test Product: Two single applications of PEP005 Topical Gel (at a concentration of 0.0025%, 0.01%, or 0.05%) were applied directly to each of the selected lesions on Day 1 and Day 2 (Treatment Arm A) or Day 1 and Day 8 (Treatment Arm B) using a positive displacement micropipette. The volume of study gel applied to each lesion was based on the longest lesion diameter as measured on Day 1, 10 µL for lesions <10 mm and 20 µL for lesions ≥10 mm.

Reference Therapy: Study vehicle gel was applied according to the guidelines used for active study gel.

Duration of Treatment: Patients received 2 single applications of study gel applied to each of the selected lesions on Day 1 and Day 2 (Treatment Arm A) or Day 1 and Day 8 (Treatment Arm B).

Criteria for Evaluation:
Efficacy: All randomized patients were evaluated for efficacy, regardless of whether or not treatment was received or administered (Intent-to-Treat [ITT] population). The histological clearance of each individual lesion was determined by assessing the extent of AK lesion clearance based on the histology results from Day 85 for patients included in the ITT population. Clinical response to treatment of each selected lesion was evaluated at each scheduled visit until End of Study (Day 85) for patients included in the mITT population. Clinical response was evaluated as: complete clearance (100% improvement, no evidence of residual disease), marked clearance (50% to 90% improvement), slight clearance (10% to 50% improvement), unchanged (±10%), worsened (clinically observable growth), or unable to be assessed (e.g., heavy scabbing, bruise, trauma, inflammatory response). Photographs were taken of AK lesions before application of study treatment at pre-dose on Day 1 and again at End of Study (Day 85) and Investigators assessed the cosmetic outcome of study treatment at End of Study (Day 85) using the photographs taken at the Day 1 visit as a reference. Cosmetic outcomes of lesional and perilesional skin were assessed at Day 85, in terms of skin texture, skin markings, scarring, skin atrophy, hypopigmentation and hyperpigmentation for patients included in the mITT population.
Safety (mITT): All patients who met the screening eligibility criteria for the study and received at least one dose of study medication were evaluated for safety. Safety was evaluated by monitoring the incidence of AEs, including the incidence and severity of local skin reactions following study drug treatment; changes in hematology, serum chemistry, and urinalysis test results; vital signs; and physical examination results during the study. The presence or absence of local skin reactions or abnormal proliferation of skin was assessed at all visits and if clinically warranted, a biopsy and/or lesion excision was to be performed during the post-treatment period followed by histological evaluation of local skin AEs that required further evaluation. Additional follow-up visits were scheduled every 7 to 14 days until local skin AEs were resolved.

Statistical Methods: The analysis in this study was primarily descriptive in nature. The study was not statistically powered to conduct formal hypothesis/inferential testing.

Summary - Conclusions:

Efficacy Results: In the histological review of punch biopsies, there was no significant difference in the presence or absence of AK lesions at the end of the study between each of the PEP005 Topical Gel dose groups and vehicle gel in either Treatment Arm A or Treatment Arm B. Between Treatment Arms, there was no significant difference in the presence or absence of AK lesions within treatment groups.

When data from both treatment arms were pooled, a statistically significant (p <0.0001) difference in the percentage of lesions cleared was observed when all treatment groups were compared. A statistically significant (p <0.0001) difference was also observed for the percentage of lesions cleared for the 0.05% PEP005 Topical Gel group when compared to vehicle gel. A statistically significant difference (p =0.0082) in the percentage of patients who had complete clearance of ≥80% of AK lesions was observed when all treatment groups were compared. A statistically significant difference (p =0.0185) was also observed for the percentage of patients in the 0.05% PEP005 Topical Gel group who had complete clearance of ≥80% of AK lesions when compared to vehicle gel. No statistically significant difference for pooled treatment arms data was observed for 100% complete AK lesion clearance for any PEP005 Topical Gel dose group, when compared to vehicle gel or when all treatment groups were compared.

Clinically significant improvement in skin texture and skin marking was seen in some patients in all dose groups and both treatment arms. The percentage of patients with significant improvement in skin texture ranged from 12.5% (Treatment Arm A; PEP005 0.01% group) to 55.6% (Treatment Arm A; PEP005 0.05% group) and the percentage of patients who had significant improvement in skin marking ranged from 11.1% (Treatment Arm B; PEP005 0.05% group) to 50.0% (Treatment Arm A; vehicle gel group). In addition, the majority (≥62.5%) of patients in all treatment groups had no scarring, skin atrophy, or skin pigmentation at Day 85.
Safety Results: Overall, the occurrence of AEs reported during the study was low (47 events in Treatment Arm A and 49 events in Treatment Arm B) and no unexpected AEs, SAEs, or trends of clinical concern were observed during the study. Although not statistically significant, an apparent dose-related trend in the incidence of AEs and number of AEs was observed for patients in PEP005 Topical Gel groups.

Overall, the majority of local skin reactions were rated as mild or moderate in severity and primarily tumor specific or with perilesional involvement for both treatment arms. The most common local skin reactions experienced by patients in both treatment arms were flaking/scaling/dryness, erythema, and scabbing/crusting. Eight patients experienced a total of 13 severe local skin reactions during the study period; six patients randomized to treatment Arm A (11 reactions) and two patients in Arm B (2 reactions). Of these eight patients, four experienced severe scabbing/crusting, two experienced severe erythema, one experienced severe itch, and one patient experienced severe flaking/scaling/dryness. No patients experienced local skin reactions of weeping/exudates, vesicles, hyperpigmentation or scarring. Two severe events of erythema were recorded for treatment Arm B; one each in the 0.0025% PEP005 and 0.01% PEP005 Topical Gel groups and all but one severe local skin reaction resolved by End of Study (Day 85).

Across treatment arms, there did not appear to be any clinically significant changes from baseline in laboratory results, vital signs, or physical examination findings during treatment.

Conclusions: This study demonstrated that two topical applications (Treatment Arm A and B) of PEP005 Topical Gel, at doses of 0.0025%, 0.01%, and 0.05%, is safe and well tolerated in patients with AK lesions. Promising results were observed in the clinical assessment of lesion clearance, although further work is necessary to define the optimal dose level and treatment regimen. In addition, a clinically significant improvement in cosmetic outcome of the selected AK lesion was observed.

Date of Report: 12 March 2008