2. Synopsis

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<thead>
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<th>Name of company:</th>
<th>Peplin Limited</th>
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<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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**Clinical Study Report Synopsis: Study PEP005-004**

**Title:** An Open-label, Dose-escalation, Cohort Study to Determine the Maximum Tolerated Dose and Safety of PEP005 Topical Gel When Applied on Day 1 and Day 2 to Actinic Keratoses on the Shoulders, Chest, Back, or Arms Followed by a Post-treatment Follow-up Period Lasting at Least Four Weeks

**Investigator:** [Redacted], MD, FACP

**Study Center:** USA

**Dates of Study:** 07 September 2005 to 14 March 2006

**Clinical Phase:** Phase IIa

**Publications:** None

**Objectives:**

The primary objective of this study was to determine the maximum tolerated dose (MTD) for PEP005 Topical Gel, administered once daily for two consecutive days, by applying 90 µL of PEP005 Topical Gel over a 3 cm x 3 cm field surrounding a target actinic keratosis (AK) lesion comprising both diseased and perilesional skin.

The secondary objectives of this study were:

1. To evaluate the clinical efficacy of PEP005 Topical Gel by determining the complete clinical response rate.
2. To determine the systemic absorption of PEP005 Topical Gel following application once daily for two consecutive days.

**Methodology:** This was an open-label, non-randomized, uncontrolled, dose-escalation, cohort study designed to determine the MTD of PEP005 Topical Gel, administered once daily for two consecutive days to patients with AK lesions.

**Number of Patients Planned and Analyzed:** Enrollment of up to 34 patients was planned. A total of 23 patients were screened, 22 patients were enrolled and analyzed for efficacy and safety, and two patients provided data for the pharmacokinetic (PK) analysis.
**Name of company:** Peplin Limited

**Name of finished product:** PEP005 Topical Gel

**Name of active ingredient:** 3-angeloyl ingenol

**Diagnosis and Main Criteria for Inclusion:** Male or female patients who were at least 18 years of age and had one AK lesion with a diameter between 3 mm and 15 mm on the shoulders, chest, back, or arms.

**Dosage, Administration, and Duration of Treatment:** A single application (90 μL) of PEP005 Topical Gel (at a dose of 0.01%, 0.025%, 0.05%, 0.075%, or 0.1%) was applied to the target AK lesion on two consecutive days using a positive displacement micropipette.

**Criteria for Evaluation:**

**Safety:** Safety was evaluated by monitoring the incidence of AEs (including the incidence and severity of local skin reactions following study drug treatment); and changes in hematology, serum chemistry, and urinalysis test results; vital signs measurements; and physical examination results during the study. Determination of MTD was the primary endpoint of this study.

**Efficacy:** Clinical response to treatment with PEP005 Topical Gel was determined by assessing the extent of AK lesion clearance at each post-Day 1 visit compared with the Baseline assessment. Clinical response was evaluated as: complete clearance (100% improvement, no evidence of residual disease), marked clearance (50-90% improvement), slight clearance (10-50% improvement), unchanged (±10%), worsened (clinically observable growth), or unable to be assessed (e.g., heavy scabbing, bruising, trauma, inflammatory response).

**Pharmacokinetics:** Samples for PK analysis were taken at baseline (before Day 1 treatment) and at 0.5, 1, 2, and 4 hours post-treatment on study Day 2 in selected patients treated at the MTD to determine the systemic absorption of PEP005 Topical Gel.

**Statistical Methods:** No hypothesis/inferential testing was conducted for this study. Data was summarized using descriptive statistics for continuous variables and using frequency and percentage for discrete variables.

**Summary of Results:**

**Safety Results:** Overall, the incidence of AEs was low. Only one patient (0.05% PEP005 Topical Gel cohort) experienced an SAE (aortic valve disease). This SAE was severe in intensity and considered unrelated to treatment with PEP005 Topical Gel.

The most common treatment emergent AEs in this study were related to application of PEP005 Topical Gel to the lesion site. Six (60.0%) patients in the 0.05% PEP005 Topical Gel, five (83.3%) patients in the 0.075% PEP005 Topical Gel, and one (33.3%) patient in the 0.01% PEP005 Topical Gel cohorts experienced application site reactions. These events included application site reaction (skin cracked on lesion site), bleeding, discharge, irritation, pain, and pruritus. Most AEs were mild or moderate in intensity. No patients discontinued treatment because of an AE.
Safety Results (continued):

Most of the patients had at least one mild skin reaction before the application of study drug (3 patients in the 0.01%, 3 patients in the 0.025%, 9 patients in the 0.05%, and 6 patients in the 0.075% PEP005 Topical Gel cohorts) and continued to have mild skin reactions over the course of the study. Patients may have had more than one local skin reaction at each time point.

Moderate local skin reactions occurred predominately in the 0.05% and 0.075% PEP005 Topical Gel cohorts. In the 0.05% PEP005 Topical Gel cohort, 1 patient on Day 1 (pre-dose), 1 patient on Day 1 (post-dose), 4 patients on Day 2, 8 patients on Day 8, 2 patients on Day 15, 0 patients on Day 29 (End of Study) had at least one moderate local skin reactions. In the 0.075% PEP005 Topical Gel cohort, 1 patient on Day 2, 5 patients on Day 8, and 2 patients on Day 15 had at least one moderate skin reaction.

Severe local skin reactions occurred only in the 0.05% and 0.075% PEP005 Topical Gel cohorts. One patient in the 0.05% PEP005 Topical Gel cohort had at least one severe skin reaction on Day 15. Two patients in the 0.075% PEP005 Topical Gel cohort had at least one severe skin reaction on Day 8.

Patients were evaluated at all study visits for the following local skin reactions: erythema, edema, erosion/ulceration, scabbing/crusting, weeping/exudates, vesicles, flaking/scaling/dryness, hypopigmentation and hyperpigmentation. Most patients had mild flaking/scaling/dryness and mild erythema before the application of PEP005 Topical Gel (at Baseline). The incidence of local skin reactions was maximal at Days 2 and 8. In addition to flaking/scaling/dryness and erythema, local skin reactions included edema, scabbing/crusting, vesicles and erosion/ulceration.

With the exception of mild flaking/scaling/dryness and mild erythema, most local skin reactions had resolved by the End of Study. Time to resolution of symptoms was longest for erythema, followed by flaking/scaling/dryness, scabbing/crusting, edema, erosion/ulceration, vesicles, and hyperpigmentation. Duration of local skin reactions ranged from 6 days to 43 days.

Most of the local skin reactions were tumor specific. Perilesional involvement was maximal on Day 2. Approximately 35% of all local skin reactions reported on Day 2 had perilesional involvement. Approximately 17% of all local skin reactions reported had perilesional involvement. About 90% of all skin reactions with perilesional involvement and about 96% with tumor specific involvement were of mild intensity.

Two patients in the 0.075% PEP005 Topical Gel cohort experienced dose-limiting toxicities (DLTs). One experienced severe scabbing/crusting and severe flaking/scaling/dryness and the other experienced severe scabbing/crusting. The MTD as determined by data collected in this study was 0.05% PEP005 Topical Gel.

There were no apparent clinically significant changes in vital signs, physical examination findings, or clinical laboratory results from Baseline to the End of Study assessment.
Efficacy Results: Clinical response to treatment with PEP005 Topical Gel was reported for the Intent-to-Treat (ITT) population. At the Day 8 assessment, complete clearance was not reported in any of the treatment groups; marked clearance was reported for two (66.7%) patients in the 0.01% PEP005 Topical Gel cohort and for one (10.0%) patient in the 0.05% PEP005 Topical Gel cohort.

At the Day 15 assessment, complete clearance was reported for three (30.0%) patients in the 0.05% PEP005 Topical Gel cohort, and two (33.3%) patients in the PEP005 Topical Gel 0.075% cohort; marked clearance was reported for two (66.7%) patients in the 0.01% PEP005 Topical Gel cohort, four (40.0%) patients in the 0.05% PEP005 Topical Gel cohort, and one (16.7%) patient in the 0.075% PEP005 Topical Gel cohort.

At the Day 29 (End of Study) assessment, complete clearance was reported in two (66.7%) patients in the 0.01% PEP005 Topical Gel cohort, one (33.3%) patient in the 0.025% PEP005 Topical Gel cohort, six (60.0%) patients in the 0.05% PEP005 Topical Gel cohort, and three (50.0%) patients in the 0.075% PEP005 Topical Gel cohort. Marked clearance was reported in only the 0.05% PEP005 Topical Gel and 0.075% PEP005 Topical Gel cohorts; two (20.0%) patients and two (33.3%) patients, respectively.

Four patients (one in the 0.05% PEP005 Topical Gel cohort and three in the 0.075% PEP005 Topical Gel cohort) had an unscheduled follow-up visit 12 to 15 days after the End of Study assessment. All four patients had an improved clinical response at the unscheduled follow-up visit. Three of the four patients had complete clearance and one had marked clearance.

Pharmacokinetics Results: Blood samples were obtained from two patients in the 0.05% PEP005 Topical Gel cohort for PK analysis. Whole blood concentrations of PEP005, and its two main isomers, PEP015 and PEP025, for both patients were below the quantifiable limit (<0.01 ng/mL) of the assay indicating that there was no detectable systemic absorption of PEP005 Topical Gel.

Conclusions: This study demonstrated 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.

Date of Report: 31 August 2006 (Final)