## SYNOPSIS

<table>
<thead>
<tr>
<th>Name of company:</th>
<th>Peplin Operations Pty Ltd</th>
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</thead>
<tbody>
<tr>
<td>Name of finished product:</td>
<td>PEP005 Topical Gel, presently referred to as PEP005 (ingenol mebutate) Gel</td>
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<tr>
<td>Name of active ingredient:</td>
<td>3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate</td>
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**Title of Study:** A Phase I, pharmacokinetic study to evaluate the extent of systemic absorption of PEP005, when applied as 0.05% PEP005 Topical Gel to a 100 cm² (5 cm x 20 cm) contiguous actinic keratosis (AK) treatment area on the extensor (dorsal aspect) forearm.

**Investigator:** Dr. Gregory Siller

**Study Centers:**
- Office of the Investigator: [Redacted], Australia (Screening and follow-up visits)
- Phase I Unit: [Redacted], Australia (Days 1, 2, and 3)

**Study Period:** 17 October 2007 to 23 April 2008

**Clinical Phase:** Phase I

**Publications:** None

**Objectives:**

The primary objective of the study was to evaluate the extent of systemic absorption of PEP005, when applied as 0.05% PEP005 Topical Gel on two consecutive days (Day 1 and Day 2) to a 100 cm² (5 cm x 20 cm) contiguous AK treatment area on the extensor (dorsal aspect) forearm.

The secondary objective of the study was to evaluate the safety and tolerability of two consecutive days’ application of 0.05% PEP005 Topical Gel, when applied to a 100 cm² (5 cm x 20 cm) contiguous AK treatment area on the extensor (dorsal aspect) forearm.

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Name of company: Peplin Operations Pty Ltd

Name of finished product: PEP005 Topical Gel, presently referred to as PEP005 (ingenol mebutate) Gel

Name of active ingredient: 3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate

Methodology: This Phase I open-label study was designed to confirm the lack of systemic absorption of PEP005 and its major metabolites PEP015 and PEP025 when 0.05% PEP005 Topical Gel was applied once daily to an unoccluded 100 cm² (0.05 μg/mm²) contiguous AK treatment area on the extensor forearm for two consecutive days. The 100 cm² contiguous treatment area served as a maximal use treatment area, utilizing the maximum AK body field-therapy concentration of PEP005 Topical Gel (i.e., 0.05% for two consecutive days). Blood samples for pharmacokinetic analysis were taken prior to and during the 24 hours following the Day 2 application. One patient was enrolled into the study during Week 1. A second patient was enrolled during Week 2 after no significant tolerability concerns were assessed in Week 1. Following assessment of the second patient at the end of Week 2, the remaining patients were enrolled into the study.

A dermatologic examination was performed by a qualified dermatologist, photographs of the selected treatment area were taken, and local skin responses (LSRs) were assessed at baseline (prior to study drug application) and at every study visit including all unscheduled visits and post-treatment follow-up visits except Day 3.

Concomitant medications were recorded. Clinical laboratory evaluations were performed at the screening visit and the Day 8 follow-up visit. Vital signs were assessed at every study visit (twice on Days 1, 2, and 3). A physical examination was performed at screening (Days -21 to -3) and Day 57. Adverse events were assessed at Day 1 to Day 57 (end of study) visits and at post-treatment follow-up visits, if necessary.

Number of Patients: Eight patients were planned so that six patients would be available for analysis. Eight patients were enrolled. Six of the eight patients completed the study and were included in the safety analysis. Three patients were treated on both study dosing days (Days 1 and 2) and therefore contributed blood specimens for the pharmacokinetic analysis.

Diagnosis and Main Criteria for Inclusion: Male patients who were at least 18 years of age with a contiguous 100 cm² treatment area containing at least five AK lesions on either the right or left extensor (dorsal aspect) forearm.

Dosage, Administration, and Duration of Treatment: PEP005 Topical Gel, 0.05%, was applied to the AK treatment area by micro-pipette on two consecutive days as 1 mL in four aliquots of 250 μL.

Criteria for Evaluation:

Safety:
The following safety parameters were assessed:
- Incidence of adverse events (AEs) throughout the study;
- Incidence rate and grade of LSRs (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosion/ulceration, hyperpigmentation, hypopigmentation, scarring) using the LSR Grading Scale (rated Grade 0 to 4). Assessments were performed at baseline (Day 1 pre-dose), Days 1 (post-dose), 2 (pre- and post-dose), 8, 29, 57, and all post-treatment follow-up and unscheduled visits;
- Fasting laboratory results (hematology, serum chemistry, and urinalysis) at screening and Day 8; and
- Vital sign measurements (at every visit [pre-dose on Days 1 and 2] and additionally at the end of the study visit on Days 1, 2, and 3) and physical examination findings at screening and Day 57 (end of study) or early termination.
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| Pharmacokinetics: |
|-------------------|------------------|
| • The pharmacokinetic (PK) blood samples (Days 1, 2, and 3) were to be quantified for PEP005 and the two major metabolites, PEP015 and PEP025. |
| • Following administration of PEP005 Topical Gel, Cmax, Tmax, and AUC(0–24) were to be evaluated for PEP005, PEP015, and PEP025 to determine systemic exposure to PEP005 Topical Gel in patients receiving two consecutive days of treatment. |

<table>
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<th>Statistical Methods:</th>
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<td>Data were summarized and listed.</td>
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<tr>
<th>Summary: Pharmacokinetic Results:</th>
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<td>All six enrolled patients received at least one dose of 0.05% PEP005 Topical Gel. Only three of the six treated patients met the requirement of the PK population and had full PK assessments; the other three patients had only partial PK assessments and were not included in the PK population.</td>
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<td>All blood samples from the six patients (three patients treated for two days; three patients treated for one day) were below the lower limit of quantification (0.100 ng/mL) for PEP005 and its metabolites PEP015 and PEP025. Therefore, no PK parameters could be calculated.</td>
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<td>This maximal use study intended to treat a larger 100 cm² contiguous treatment area on the extensor forearm of a single arm with 0.05% PEP005 Topical Gel, once daily for two consecutive days. Patients in this study had more intense LSRs than were observed in earlier studies treating smaller 25 cm² areas. Because of these more intense responses, only 50% of patients (three out of six) were able to tolerate two consecutive days of treatment. Although LSRs and AEs precluded three patients from being treated on the second day, reactions were similar to those observed in earlier AK field-therapy studies treating 25 cm² areas of skin (i.e., Protocol PEP005-006), with peak composite LSR scores on or around Day 8 and limited or no residual AEs and/or LSRs at the end of the study.</td>
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<td>The mean composite LSR and peak score were able to describe the general course of LSR events in this study. Mean composite LSR scores generally peaked on or before Day 8, showed marked improvement by Day 29, and most returned to baseline levels by Day 57 (end of study). It should be noted that there were several unscheduled visits that occurred and that only six patients that were assessed. Three patients (Patients and were followed for LSRs after Day 57 (refer to pigmentary LSR below), but there were no LSRs greater than Grade 2 following the Day 57 assessment, with the exception of Patient (again, refer to pigmentary LSR below).</td>
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<td>Erythema and flaking/scaling were the most frequently occurring LSRs. Both erythema and flaking/scaling had the highest rated post-dose LSR grade. Four patients (66.7%) had a Grade 4 LSR for both erythema and flaking/scaling.</td>
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Vesiculation/pustulation was recorded for the first time at Day 2 pre-dose in four patients (66.7%), and by a fifth patient at Day 6 (unscheduled). The vesiculation/pustulation continued in three patients to Day 8 and resolved by Day 29 (note that there were no scheduled study visits between Day 8 and Day 29). The highest rated post-dose LSR for vesiculation/pustulation was recorded as a Grade 4 (three patients; 50%). The investigator assessed one of the three patients with vesiculation/pustulation as having moderate cellulitis and treated the patient successfully with oral antibiotics.

Scarring rated no higher than a Grade 1 LSR throughout the study and already existed in three patients (50%) at baseline (Day 1 pre-dose). The incidence of scarring decreased during the study and was no longer recorded in any patient from Day 2 onwards. Three patients (50%) actually improved their scarring LSR rating from baseline.

Pigmentary changes were observed in this study. Five patients (83.3%) had either hypopigmentation or hyperpigmentation noted at baseline. By Day 57 (end of the study), two patients (33.3%; [redacted] and [redacted]) had improved, one patient (16.7%; [redacted] was unchanged, and three patients (50.0%; [redacted], [redacted] and [redacted]) had pigmentary changes greater than baseline at Day 57 that were followed until improvement to baseline levels or for a period of four months following the Day 57 visit. Of the three patients, only one ([redacted]) had pigmentary change recorded out to Day 154 that was one grade above baseline (Grade 2). The other two patients either returned to baseline ([redacted]) or improved ([redacted]) from their baseline value. Most of the pigment changes described above were in the direction of hypopigmentation. Hyperpigmentation was reported only in one patient ([redacted]), who had an overall pigmentation Grade 3 at baseline that improved to Grade 0 by Day 8.

There were two instances of patients with abnormal proliferation within the treatment area. One patient ([redacted]) with a history ([redacted]), presented with keratoacanthoma on Day 15 post-treatment (lasted for approximately one month) and squamous cell carcinoma (Bowen’s disease) on Day 57 post-treatment. No action was taken for the keratoacanthoma following a confirmatory biopsy, and the squamous cell carcinoma was excised on Day 92 post-treatment and remained clear at follow-up on Day 183. The investigator felt that the keratoacanthoma was definitely related to study treatment and the Bowen’s disease was possibly related to study treatment. Another patient ([redacted]) was diagnosed with lentigo following a confirmatory biopsy (which cleared the lesion) on Day 36 post-treatment. The investigator recorded the lentigo as possibly related to study treatment.

There was one SAE recorded in this study for the patient with Bowen’s disease (described above). There were no patient deaths in this study, and no patients were discontinued from the study due to an AE, although three patients did not receive study drug on Day 2 due to either a treatment emergent adverse event (TEAE) or an LSR. All AE s and SAEs resolved and all LSRs resolved to baseline values or better, except for the one case of pigmentation change (described above) for Patient ([redacted]) and one patient ([redacted]) who had a baseline erythema Grade 0 that remained a Grade 1 at the end of study (actual grading was assessed on Day 44). The two patients who did discontinue from the study, did so during the screening period, one due to laboratory abnormalities and one withdrawal of consent.
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Summary table referring to Part of the dossier  
Volume: Page: 

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Conclusions:
The PK data suggest that treatment of a 100 cm² area of skin with 0.05% of PEP005, once daily for one or two consecutive days does not demonstrate systemic absorption of PEP005 or its metabolites PEP015 or PEP025.

More intense LSRs were observed in this study treating 100 cm² areas than in earlier studies treating smaller, 25 cm² areas. Because of these more intense responses, only 50% of patients (three out of six) were administered two consecutive days of treatment. Although LSRs and AEs precluded these three patients from being treated on two consecutive days, all reactions observed in this study were similar to those observed over a 25 cm² treatment area of skin (i.e., Protocol PEP005-006). This study, treating larger areas of skin demonstrated a greater mean composite LSR intensity at peak and a longer time to have LSRs completely resolve. It should be noted that all LSRs, except for pigmentary changes, decreased by Day 29 and resolved to baseline or better by Day 57 (end of study). The three patients with hypopigmentation above baseline levels at Day 57 were followed until resolution to baseline value. Reassuringly, all LSR pigmentation changes eventually resolved, with the exception of one patient who had pigmentary change that was one grade above baseline (baseline, Grade 1; Day 154, Grade 2) at the last evaluation. Of note, 50% (three of six) of patients reported an ultimate improvement in their pigmentary change, compared to their baseline (Day 1 pre-dose) score. There was no treatment emergent scarring observed in this study, and 50% (three of six) of patients had actually improved scarring from baseline to end of study. All TEAEs and SAEs reported for patients in this study resolved. Overall, there were no long term sequelae to treating a 100 cm² area of skin in this population of six patients with sun damaged skin, wherein 83.3% (five out of six patients) had approximately 21 to 50 AK lesions on their extremities at the time of study enrollment.

In terms of the abnormal proliferation observed in this study, a feature of topical therapies for the treatment of AK is the uncovering of subclinical lesions (so-called treatment-emergent lesions). Patient developed abnormal proliferation (keratoacanthoma and Bowen’s disease) within the treatment area during this study. Although the abnormal proliferation was deemed to be related to the study treatment by the investigator, it is in the opinion of the Sponsor that there were multiple long-standing risk factors reported in the patient’s medical history that make it problematic to assign a causal relationship between drug therapy and the emergence of these lesions.

The Sponsor feels that there were no long-term or unexpected sequelae that manifested during this study; however, further evaluation of 0.05% Topical Gel is needed to assess the maximal area of skin that can safely be treated with PEP005 Topical Gel due to the small number of patients treated once daily for two consecutive days over a 100 cm² contiguous area in this study. An open-label, dose-area escalation, cohort study will be conducted to further assess this question prior to conducting another maximal use PK study.

Date of Report: January 22, 2009