## SYNOPSIS

<table>
<thead>
<tr>
<th>Sponsor:</th>
<th>Peplin Operations Pty Ltd</th>
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<tbody>
<tr>
<td><strong>Name of Finished Product:</strong></td>
<td>PEP005 (ingenol mebutate) Gel</td>
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<td><strong>Name of Active Ingredient:</strong></td>
<td>Ingenol Mebutate</td>
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<tr>
<td><strong>Title:</strong></td>
<td>A randomized, double-blind, vehicle-controlled study to evaluate the pharmacokinetics of PEP005 (ingenol mebutate) Gel, 0.05%, when applied in a maximal use setting to the dorsal aspect of the forearm in patients with actinic keratosis</td>
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<td><strong>Investigators and Sites:</strong></td>
<td>Single site in the US (refer to Appendix 16.1.4.1)</td>
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<td><strong>Publications:</strong></td>
<td>None</td>
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<td><strong>Study Period:</strong></td>
<td>First patient randomized: March 18, 2009 Last patient completed Day 57: May 27, 2009</td>
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<td><strong>Phase of Development:</strong></td>
<td>2</td>
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<td><strong>Objectives:</strong></td>
<td>The primary objective was to evaluate the potential for systemic exposure of ingenol mebutate when applied in a maximal use setting to the dorsal aspect of the forearm in patients with actinic keratosis. The secondary objectives were to evaluate the safety and efficacy of PEP005 Gel, 0.05%, when applied in a maximal use setting to the dorsal aspect of the forearm in patients with actinic keratosis.</td>
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<td><strong>Methodology:</strong></td>
<td>This was a randomized, double-blind, vehicle-controlled study. Following screening for eligibility, patients were randomized, through an Interactive Voice Response (IVR) system, to receive either PEP005 Gel, 0.05%, or vehicle gel in a 4:1 ratio, respectively, on study Day 1. Study medication was applied on Days 1 and 2 in the clinic, by site staff. Pharmacokinetic (PK) blood samples were collected for all patients prior to study medication application on Day 1, through to 24 hours following the Day 2 study medication application. Study visits for safety and efficacy assessments occurred on Days 2, 3, 8, 15, 29 and 57 (study exit). Post-study follow-up visits were required for all patients with unresolved treatment-related adverse events (AEs), local skin responses (LSRs), pigmentation or scarring, greater than observed at baseline, at the Day 57 visit.</td>
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<td><strong>Number of Patients (Planned and Analyzed):</strong></td>
<td>Approximately 15 patients were planned for enrollment. A total of 16 patients were randomized (analyzed) (13 patients randomized to PEP005 Gel and three to vehicle gel). All 16 patients completed the study to Day 57.</td>
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<td><strong>Diagnosis and Main Criteria for Inclusion:</strong></td>
<td>Male or female patients at least 18 years of age with multiple actinic keratosis (AK) lesions within a contiguous 100 cm² treatment area on the dorsal aspect of one forearm.</td>
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<td><strong>Test Product and Reference Therapy, Dose, Mode of Administration, and Lot:</strong></td>
<td>Study medication was supplied as PEP005 Gel, 0.05% (Lot: AKW-C) test product, or vehicle gel (Lot: ZMAB-C) reference therapy. Study medication was applied topically to the 100 cm² selected treatment area by the clinic site staff, once daily for two consecutive days (Days 1 and 2).</td>
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Pharmacokinetic Evaluation:
Blood samples for PK analysis were collected prior to study medication application on Day 1, prior to study medication application on Day 2 (+24 hr Day 1), and at 30 minutes, 1, 2, 4, 8, 12 and 24 hours following study medication application on Day 2.
Whole blood samples were quantified (Cmax, Tmax and AUC(0–24)) for ingenol mebutate and its primary metabolites, PEP015 and PEP025 (lower limit of quantification [LLOQ] = 0.1 ng/mL).

Randomization Scheme:
Patients were randomized through an IVR system to receive either PEP005 Gel, 0.05%, or vehicle gel in a 4:1 ratio, respectively. Approximately 12 patients were to be treated with PEP005 Gel and approximately three patients were to be treated with vehicle gel.

Criteria for Evaluation:
The primary criteria for evaluation were whole blood samples, quantified (Cmax, Tmax and AUC(0–24)) for ingenol mebutate and PEP015 and PEP025.
The secondary criteria for evaluation were:
• Incidence rate of AEs, serious adverse events (SAEs) and AEs leading to discontinuation through Day 57;
• Incidence rate and grade of LSRs, pigmentation and scarring, following study treatment through Day 57;
• Complete clearance rate, defined as no clinically visible AK lesions in a 25 cm² area within the selected treatment area; and
• Percentage (%) reduction in AK lesions at Day 57, compared to baseline, in a 25 cm² area within the selected treatment area.

Statistical Methods:
Results were summarized into tabulations, case listings, plots, and histograms for comparison. Descriptive summaries were created to include the mean, standard deviation, median, and range for continuous variables, and counts and percentages for categorical variables.
The PK analysis was performed using the PK population, defined as all randomized patients who had received at least one dose of study medication with at least one post-baseline PK blood sample.
The safety analysis was based on the safety population, defined as all randomized patients who had received at least one dose of study medication and who had at least one post-baseline safety evaluation. In the safety population, patients were counted in the group in which they were treated.
The efficacy analysis was based on the intent-to-treat (ITT) population, defined as any patient randomized to the study.

Summary of Results:
Pharmacokinetic Results:
No systemic absorption was detected. Levels of ingenol mebutate and its acyl isomers were below the LLOQ in samples from all patients following two consecutive once-daily applications of PEP005 Gel, 0.05%.
Efficacy Results:
AK lesion clearance was assessed at Day 57 in a 25 cm² contiguous area of skin located within the larger treatment area.
Of the patients who received treatment with PEP005 Gel, 0.05%, 77% (10/13) had complete clearance of all AK lesions, and all patients had partial clearance. None of the three patients treated with vehicle gel had complete or partial clearance of their AK lesions.

The percentage change from baseline in the total AK lesion count in the selected 25 cm² area was also assessed at Day 57. The median percentage reduction in AK lesion count was 100% in patients treated with PEP005 Gel, 0.05%, and zero in those patients treated with vehicle gel.

Safety Results:

PEP005 Gel, 0.05%, appeared to be safe and well tolerated when applied in a maximal use setting to the dorsal forearm in patients with AK. All patients received the scheduled treatment of two consecutive once-daily doses of study medication. Three patients (23%; 3/13) treated with PEP005 Gel, 0.05%, experienced a total of five AEs and two patients (67%; 2/3) treated with vehicle gel experienced a total of two AEs. The only AE category (by system organ class) reported in more than one patient treated with PEP005 Gel was 'injury, poisoning and procedural complications' (15%; 2/13). No individual AE by preferred term was reported in more than one patient.

Of the seven reported AEs, one (mild diarrhea) was deemed "possibly" treatment-related; however, upon unblinding, this patient was found to be randomized to vehicle gel. One patient experienced an insect bite within the treatment area. No SAEs occurred in this study.

Among patients who received active treatment, the mean composite LSR score was 0.1 at baseline, reached a maximum of 6.6 on Day 3, and returned to pretreatment levels by Day 57. In patients who received vehicle gel, the mean composite LSR score was 0.3 at baseline, and zero throughout the remainder of the study.

All patients treated with PEP005 Gel, 0.05%, experienced erythema and flaking/scaling. Swelling and vesiculation/pustulation were reported in 69% (9/13) and 54% (7/13) of patients, respectively. One patient had Grade 1 erythema at Day 57, while all other LSRs resolved during the study. Grade 4 erythema and/or flaking/scaling occurred in five of 13 patients (38%) following treatment with active medication. All Grade 4 LSRs resolved by Day 57 on study. No LSRs occurred following treatment in the vehicle group.

Compared to baseline, there were no changes in hypopigmentation or hyperpigmentation at Day 57. Transient pigmentation changes occurred in two patients treated with PEP005 Gel, 0.05% (one case each of Grade 1 hypopigmentation and Grade 1 hyperpigmentation, both of which resolved by the end of the study). No patients had scarring or abnormal proliferation.

There were no clinically relevant changes in vital signs or physical examination findings. Patient 108 had a moderate gamma-glutamyl transpeptidase (GGT) increase on Day 8 that was considered unrelated to treatment with PEP005 Gel, 0.05%.

Conclusion:
The results of this study demonstrate that there is no evidence of systemic absorption when PEP005 Gel, 0.05%, is applied once daily for two consecutive days to a 100 cm² contiguous AK treatment area on the dorsal forearm. PEP005 Gel, 0.05%, appears safe and well tolerated in this maximal use setting.

Final Report Date: January 28, 2010