**SYNOPSIS**

<table>
<thead>
<tr>
<th>Sponsor:</th>
<th>Peplin Operations Pty Ltd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Finished Product:</td>
<td>PEP005 (ingenol mebutate) Gel</td>
</tr>
<tr>
<td>Name of Active Ingredient:</td>
<td>Ingenol Mebutate</td>
</tr>
<tr>
<td>Title:</td>
<td>A multicenter, randomized, double-blind, vehicle-controlled, dose-ranging study to evaluate the safety and efficacy of 0.005%, 0.01% and 0.015% PEP005 Topical Gel when used to treat actinic keratoses on the head (face or scalp)</td>
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<tr>
<td>Investigators and Sites:</td>
<td>Multicenter in the United States and Australia (refer to Appendix 16.1.4.1)</td>
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<tr>
<td>Publications:</td>
<td>None</td>
</tr>
</tbody>
</table>
| Study Period: | First patient randomized: 24 June 2008  
Last patient completed Day 57: 20 October 2008 |
| Phase of Development: | 2 |
| Objectives: | The primary objectives of the study were to evaluate the safety, toleration, and efficacy of PEP005 Gel, 0.005%, 0.01%, and 0.015%, compared to vehicle gel, administered once daily as either a two or three consecutive day treatment regimen, to a 25 cm² contiguous actinic keratoses (AK) treatment area on the face or scalp as measured by the following:  
- Primary safety and tolerability variables:  
  - Incidence of adverse events (AEs) and serious adverse events (SAEs) recorded throughout the study;  
  - Incidence and severity (i.e., grade) of local skin responses (LSRs), and incidence of pigmentation and scarring following study medication application; and  
  - Dosing compliance/tolerability, defined as the proportion of patients completing assigned treatment regimen (two or three day treatment).  
- Primary efficacy variable:  
  - Complete clearance rate, defined as the proportion of patients at the Day 57 visit with no clinically visible AK lesions in the selected treatment area.  
- The secondary objective of the study was to evaluate the efficacy of PEP005 Gel, 0.005%, 0.01%, and 0.015%, compared to vehicle gel, administered once daily as either a two or three consecutive day treatment regimen, to a 25 cm² contiguous AK treatment area on the face or scalp as measured by the following:  
- Secondary efficacy variable:  
  - Partial clearance rate, defined as the proportion of patients at the Day 57 visit with a 75% or greater reduction in the number of AK lesions identified at baseline, in the selected treatment area. |
| Methodology: | This was a multicenter, randomized, double-blind, vehicle-controlled, dose-ranging study.  
Patients were screened and randomized to one of three PEP005 Gel concentrations (0.005%, 0.01%, 0.015%) or vehicle gel and were treated once daily for either two or three consecutive days. Patients were evaluated on the basis of safety, tolerability, and efficacy for 57 days following study treatment. Patient satisfaction with treatment and quality of life were also evaluated at time points throughout the study.  
Poststudy followup visits were required if patients had unresolved, treatment-related adverse events, LSRs, pigmentation and/or scarring at Day 57. |
Number of Patients (Planned and Analyzed):
Approximately 240 patients were planned for enrollment (30 patients per treatment group; eight treatment groups). A total of 265 patients were randomized and 260 patients completed the study. All randomized patients were included in the intent-to-treat (ITT) population; 250 patients were included in the per-protocol (PP) population. The safety population included 264 patients.

Diagnosis and Main Criteria for Inclusion:
Male or female patients at least 18 years of age with four to eight clinically typical, visible, and discrete AK lesions within a contiguous 25 cm² treatment area on the face or scalp.

Dosage, Administration and Duration of Treatment:
Study medication was supplied as: PEP005 Gel, 0.005%, 0.01%, 0.015%, and vehicle gel.

One lot of study medication was used for each concentration of PEP005 Gel and for vehicle gel. The following lots were used: ZMAB-C (vehicle); AEG-C (0.005%), AHB-C (0.015%); and ADB-C (0.01%).

Study medication was packaged individually for each patient in a study medication kit containing two or three unit-dose-tubes. Each tube contained PEP005 Gel or vehicle gel. Study medication was applied topically to the selected treatment area by the patient, at home, once daily on Days 1 and 2 or Days 1, 2, and 3, as directed by the Investigator.

Randomization Scheme:
Patients were assigned to a treatment group by an Interactive Voice Response/Interactive Web Response (IVR/IWR) system. Patients were randomized centrally, to treatment in a 1:1:1:1:1:1:1:1 fashion and were stratified across treatment groups (as per the table below) based on location of AK lesions on the head (i.e., face or scalp). Enrollment was controlled so that approximately 20% of the patients enrolled were treated on the scalp and approximately 80% of the patients enrolled were treated on the face.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Study Medication Concentration</th>
<th>Regimen</th>
<th>Number of Patients</th>
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<tbody>
<tr>
<td>1</td>
<td>0.005%</td>
<td>Day 1, 2</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>0.01%</td>
<td>Day 1, 2</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>0.015%</td>
<td>Day 1, 2</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>vehicle gel</td>
<td>Day 1, 2</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>0.005%</td>
<td>Day 1, 2, 3</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>0.01%</td>
<td>Day 1, 2, 3</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>0.015%</td>
<td>Day 1, 2, 3</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>vehicle gel</td>
<td>Day 1, 2, 3</td>
<td>30</td>
</tr>
</tbody>
</table>

Statistical Methods and Criteria for Evaluation:
The primary efficacy analyses were based on the PP population. The PP population included patients without major protocol violations; patients were analyzed according to the actual treatment received. Secondary analyses were based on the ITT population, defined as all patients randomized; patients were analyzed according to the treatment to which they were randomized.

The safety analyses were based on the safety population. The safety population included patients who received at least one dose of study medication; patients were analyzed according to the actual treatment received.
For the analyses of the efficacy variables and LSRs, all missing values due to patient early termination from the study were imputed using the last observation carried forward (LOCF) method. For each patient, the baseline values were defined as those values recorded at Day 1 prior to dosing or screening, as appropriate.

All hypotheses were tested for statistical significance with two-tailed tests. Results of all tests were considered statistically significant if their p-value was less than or equal to 0.05, with the exception of Hochberg's multiple comparison procedure. Results of Hochberg's multiple comparisons were considered statistically significant if the p-value was less than or equal to 0.05, 0.025, or 0.0167, according to the procedure.

**Efficacy:** The primary efficacy endpoint was the complete clearance rate of AK lesions at Day 57. A Cochran-Mantel-Haenszel (CMH) test, adjusting for treatment area (face, scalp), was used to test for treatment effect. The secondary efficacy endpoint was the partial clearance rate of AK lesions at Day 57. The statistical analysis was the same as the one used for the primary efficacy endpoint.

Dose effect was explored by inspection of observed means or rates for the PEP005 Gel and vehicle gel groups within each treatment regimen.

**Safety:** The primary safety endpoints were the rates of patients who had (1) one or more AEs; (2) SAEs; and (3) AEs leading to discontinuation of study medication; the percentage of patients who had one or more LSRs and severity of responses and/or pigmentation and scarring; and patient compliance/tolerance to the regimen. Other safety endpoints of interest were laboratory results and vital sign measurements.

**Patient Reported Outcomes:** The results were summarized for the Treatment Satisfaction Questionnaire for Medication (TSQM) and the Skindex-16 Dermatology Survey. The derived scores were analyzed using an analysis of variance (ANOVA) to test for treatment effect.

**Summary of Results:**

**Efficacy Results**

The primary efficacy endpoint was complete AK lesion clearance on the face and scalp at Day 57. Five of the six PEP005 Gel groups demonstrated statistically significant, higher complete clearance rates versus vehicle gel (CMH test corrected for multiple comparisons) based on both the PP and ITT populations.

Observed complete clearance rates were concentration and treatment regimen-dependent with the highest observed complete clearance rates in the 0.015% two-day and three-day groups. The observed complete clearance rates for PEP005 Gel at Day 57 for the ITT population ranged from 15% in the 0.005% two-day group to 50% in the 0.015% three-day group. The trends for complete clearance rates on the face and scalp, assessed separately, were similar to those observed for the face and scalp combined. Complete clearance rates for scalp-treated patients were lower compared to face-treated patients; however, the sample sizes were small (< 10 patients per group). Similarly, data trends toward concentration and treatment-regimen dependence were weaker than those for face-treated and combined face and scalp-treated patients.

The secondary efficacy endpoint was partial (≥ 75% reduction) AK lesion clearance at Day 57. Five of the six PEP005 Gel groups demonstrated statistically significant, higher partial clearance rates versus vehicle gel (CMH test corrected for multiple comparisons) based on both the PP and ITT populations. Partial clearance rates were concentration and treatment regimen-dependent with the highest observed complete clearance rates in the 0.015% two-day and three-day groups. The observed partial clearance rates for PEP005 Gel at Day 57 for the ITT population ranged from 33.3% in the 0.005% two-day group to 71.9% in the 0.015% three-day group. Similar to what was observed for complete clearance rates, when separated by anatomic treatment location (face and scalp), the partial clearance rates trended toward concentration and treatment-regimen dependence.

The percent changes in number of AK lesions for the face and scalp combined were also concentration and treatment regimen-dependent, with the greatest median percent reduction seen in the 0.015% three-day group.
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Page: (84.5%). Median percent reduction in number of AK lesions was also similar when face-treated and scalp-treated patients in the 0.015% three-day group were analyzed separately (87.5% and 80.0%, respectively).

While study results support a concentration and treatment regimen-dependent relationship across the eight treatment groups, complete and partial clearance rates and median percent reduction in number of AK lesions in the 0.01% three-day treatment group were lower compared to other PEP005 Gel three-day groups. Statistically significant, higher mean patient global satisfaction scores, measured by the TSQM, were shown for all PEP005 Gel groups, relative to vehicle gel; the mean satisfaction scores were highest in the 0.01% and 0.015% two-day groups, followed by the 0.01% and 0.015% three-day groups. No statistically significant differences from vehicle gel were noted for the three domains (symptoms, emotions, and functioning) of the Skindex-16 Dermatology Survey for the face and scalp at Day 57.

In the subgroup analyses, there were statistically significant differences in both the complete clearance and partial clearance rates for the following subgroups: females had higher rates than males (complete clearance, p = 0.0054; partial clearance, p = 0.0142) and patients with ≤ six baseline lesions had higher rates than patients with ≥ seven baseline lesions (complete clearance, p = 0.0067; partial clearance, p = 0.0172). Additionally, the face demonstrated a statistically significant, higher partial clearance than the scalp (p = 0.0141). There were no other statistically significant differences in complete or partial clearance rate for any of the other subgroups: age, Fitzpatrick skin type, or geographic location.

Safety Results

PEP005 Gel was well tolerated when applied once daily for two or three consecutive days. Overall, the compliance to the treatment regimen, for all treatment groups was 97.4% (258 of 265 patients).

Three patients had four SAEs (fever in one patient not randomized; gastroesophageal reflux and muscle strain in one patient; and death due to coronary artery atherosclerosis and hypertension in one patient). None of these events were considered related to study medication.

Application site reactions were the most common treatment-related AEs reported. Irritation and pruritus at the application site were most common, followed by application site discomfort, swelling, and pain. A lower percentage of patients in the two-day groups had application site reactions than in the three-day groups. In all cases, the treatment-related events resolved without any sequelae.

LSRs (grade 0-4) were assessed at baseline, Day 1 (pre-dose), and each subsequent study visit for the presence and grade (0 to 4) of the following LSRs: erythema, flaking/scaling, crusting, swelling vesiculation/pustulation, and erosion/ulceration. A composite LSR score (0 to 24), reflecting the sum of each individual LSR grade, was calculated for each patient at each visit. The most common LSRs for all patients were flaking/scaling, erythema, and crusting. Grade 4 LSRs were reported primarily in the 0.015% three-day group, and all Grade 4 LSRs resolved to baseline levels or lower by Day 57, except for one patient (Patient 07-002) who had Grade 3 erythema and flaking/scaling at Day 57.

Mean composite LSR scores were concentration and treatment-regimen dependent with a peak score occurring at Day 4 in all PEP005 Gel groups. The highest peak mean composite LSR score (9.8) was observed in the 0.015% three-day group. Mean composite LSR scores returned to baseline levels or lower by Day 57.

No apparent differences were observed in peak mean LSR scores between face-treated and scalp-treated patients; however, peak mean composite LSR scores were higher for the face than they were for the scalp. Regardless of peak scores, the mean LSR scores for both the face and scalp returned to baseline grade or better at Day 57.

Pigmentation (hyperpigmentation and hypopigmentation) assessments remained unchanged from baseline in 75% of patients. None of the cases of pigmentation were considered clinically important by the Investigator.
Scarring assessments remained unchanged from baseline in 99% of patients. Scarring improved in all three patients (< 1%) with changes in scarring compared to baseline assessments.

No patients had abnormal proliferation within the treatment area during the study. Administration of PEP005 Gel had no apparent impact on laboratory tests or vital sign values.

**Conclusion:**

PEP005 Gel, at a concentration of 0.01% once daily for two consecutive days and at a concentration of 0.015% once daily for two or three consecutive days, demonstrated statistically significant and clinically meaningful improvements in complete clearance of AK lesions on the face and scalp compared to vehicle gel. The median number of AK lesions was reduced with all PEP005 Gel concentrations and regimens tested with the highest reduction in the 0.015% two-day and three-day groups.

Efficacy results for treatment on the face and scalp separately were consistent with what was seen for both the face and scalp combined, with generally lower clearance rates and smaller magnitudes of percent reduction in number of AK lesions for the scalp compared to the face.

Safety and efficacy appear to be concentration and treatment regimen-dependent.

At all treatment regimens evaluated (0.005%, 0.01%, and 0.015% applied once daily for two or three consecutive days), PEP005 Gel appears safe and well-tolerated when used to treat AK lesions on the face or scalp.