A multi-center, Randomized, parallel group, double-blind, vehicle-controlled study to evaluate the Efficacy and safety of PEP005 (ingenol mebutate) Gel, 0.015% in patients with actinic keratoses ON the head (face or scalp) (REGION-IIa)

Investigators and Sites: Multi-center in the United States and Australia (refer to Appendix 16.1.4.1)

Publications: None

Study Period:
First patient randomized: 05 June 2009
Last patient completed Day 57: 10 September 2009

Phase of Development: 3

Objectives:
To evaluate the efficacy and safety of PEP005 Gel, 0.015%, compared to vehicle gel when administered once daily for three consecutive days to a contiguous 25 cm² area of skin on the head (face or scalp).

Methodology:
This was a multi-center, randomized, parallel group, double-blind, vehicle-controlled study. Patients were randomized to receive treatment with PEP005 Gel, 0.015%, or vehicle gel once daily for three consecutive days. Study medication was patient-applied at home on Days 1, 2 and 3. Subsequent followup visits for safety assessments were conducted on Days 4, 8, 15, 29 and 57. Efficacy assessments were conducted at baseline (Day 1 pre-dose) and on Day 57 (End of Study). Patient-reported treatment satisfaction was assessed on Day 57 and Quality of Life (QOL) assessments were conducted at baseline and on Days 8, 29 and 57. Patients completed the study on Day 57.

Poststudy follow-up visits were required every 7 to 28 days for all patients who had unresolved treatment related adverse events (AEs) or local skin responses (LSRs) at Day 57. Patients with unresolved hypopigmentation or hyperpigmentation and/or scarring greater than baseline were required to undergo further poststudy followup every 28 days until resolution or for a period of six months postbaseline (an additional four visits) unless deemed clinically insignificant.

Number of Patients (Planned and Analyzed):
Planned: Approximately 250 patients (125 per treatment arm) were planned for enrollment.
Analyzed: A total of 269 patients were randomized (135 to PEP005 Gel 0.015% and 134 to vehicle gel); 259 patients completed the study. All randomized patients were included in the intent-to-treat (ITT) population; 246 patients were included in the per-protocol (PP) population. The safety population included 267 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 actinic keratoses (AK) lesions within a contiguous 25 cm² treatment area on the head (face or scalp).

Test Product and Reference Therapy, Dose, Mode of Administration and Lots:
Test product: PEP005 Gel, 0.015% (Lot ).
Reference therapy: Vehicle gel (Lots  and ).
Study medication was packaged individually for each patient in a study medication kit containing three unit-dose tubes. Each unit-dose tube contained PEP005 Gel 0.015% or vehicle gel.
**Peplin PEP005-016 Synopsis**

**PEP005 (ingenol mebutate) Gel**

**Sponsor:** Peplin Operations Pty Ltd

<table>
<thead>
<tr>
<th>Individual Study Table Referring to Part of the Dossier</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name of Finished Product:</strong> PEP005 (ingenol mebutate) Gel</td>
</tr>
<tr>
<td><strong>Name of Active Ingredient:</strong> Ingenol Mebutate</td>
</tr>
</tbody>
</table>

### Duration of Treatment:
Study medication was applied topically to the selected treatment area by the patient, at home, once daily on study Days 1, 2 and 3.

### Randomization Scheme:
Patients were randomized centrally to treatment in a 1:1 ratio through an interactive voice/web response (IVR/IWR) system. Randomization was stratified by investigational site and by the location of the treatment area (face or scalp). Enrollment was controlled so that approximately 20% of patients were treated on the scalp and approximately 80% of patients were treated on the face. The IVR/IWR system assigned a study medication kit number for each patient randomized into the study.

### Criteria for Evaluation:

**Efficacy:**

**Primary Endpoint:**
Complete clearance rate of AK lesions at the Day 57 visit. A patient with no clinically visible AK lesions in the selected treatment area was defined to have complete clearance.

**Secondary Endpoint:**
Partial clearance rate of AK lesions at the Day 57 visit. A patient with a 75% or greater reduction in the number of clinically visible AK lesions identified at baseline, in the selected treatment area was defined to have partial clearance.

**Additional Endpoint:**
The percent change from baseline to Day 57 in the total number of AK lesions.

**Exploratory:**
Patient-reported outcomes, including the Treatment Satisfaction Questionnaire for Medication (TSQM) at Day 57 and the Skindex-16 Dermatological Survey at baseline and Days 8, 29, and 57.

**Safety:**
- Incidence rate of AEs, serious adverse events (SAEs) and AEs leading to discontinuation of study medication as recorded throughout the study;
- Incidence rate and grade of LSRs, pigmentation and scarring following study treatment;
- Results of clinical laboratory tests, vital signs, physical examinations, and electrocardiogram (ECG) findings.

### Statistical Methods:
The primary efficacy analysis was based on the intent-to-treat (ITT) population. In the ITT population, patients were counted in the treatment group to which they were randomized, regardless of receiving any dose of study medication.

For the analyses of complete and partial clearance, all missing values were imputed using last observation carried forward (LOCF). Baseline data were carried forward if no postbaseline data existed for the patient. That is, those patients were considered to have not achieved complete or partial clearance.

The safety analysis was based on the safety population, which was defined as all randomized patients who received at least one dose of study medication and had at least one postbaseline safety evaluation. In the safety population, patients were analyzed according to the actual treatment received.

All treatment comparisons were tested with two-tailed tests and a 0.05 significance level.
Efficacy:
The primary efficacy endpoint was complete clearance rate at Day 57 of all clinically visible AK lesions in the selected treatment area. The complete clearance rate was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test, stratified by analysis site. The secondary efficacy endpoint was the partial clearance rate of AK lesions at Day 57. The statistical analysis was the same as that used for the primary efficacy endpoint.

An additional efficacy endpoint was the percent change from baseline to Day 57 in the total number of AK lesions. The percent change from baseline in the number of AK lesions was summarized for each treatment group. Summaries were also provided by each anatomical location.

Patient-Reported Outcomes:
The TSQM transformed scores at Day 57 and the Skindex-16 Dermatological Survey transformed scores at baseline and Days 8, 29, and 57 were summarized by treatment group. The transformed scores were treated as a continuous variable and analyzed using analysis of variance (ANOVA) with treatment, anatomical location, and analysis site as factors to test for treatment effect.

Safety:
The safety endpoints included: incidence of patients who experienced AEs, SAEs and AEs leading to discontinuation of study medication; incidence and grade of LSRs and/or pigmentation/scarring; changes in clinical laboratory tests, vital signs, physical examinations, and ECG findings. The treatment effect was explored by inspection of observed means or rates for the treatment groups.

Summary of Results:

Summary of Results:

Efficacy:
The primary efficacy endpoint was complete AK lesion clearance overall (face and scalp combined) at Day 57. The PEP005 Gel group demonstrated a statistically significant, higher complete clearance rate versus vehicle gel (37% compared to 2%, p<0.001, CMH test stratified by analysis site) based on the ITT population. The results of the PP population were consistent with the results of the ITT population. For patients treated on the face (n = 109 for each treatment group), PEP005 Gel also demonstrated a statistically significant, higher complete clearance rate compared to vehicle gel (42% versus 3%, p=0.001, Fisher's Exact test). For scalp-treated patients (n = 26 for PEP005 Gel; n = 25 for vehicle gel), the difference between the treatment groups was not statistically significant but was numerically in favor of PEP005 Gel (15% versus 0%, p=0.110, Fisher's Exact test).

The secondary efficacy endpoint was partial (≥75% reduction) AK lesion clearance at Day 57. Consistent with the primary endpoint, the PEP005 Gel group demonstrated a statistically significant, higher partial clearance rate versus vehicle gel (60% compared to 7%, p<0.001, CMH test stratified by analysis site) based on the ITT population. The results of the PP population were consistent with the results of the ITT population. Patients treated on the face with PEP005 Gel also demonstrated statistically significant, higher partial clearance rates than vehicle gel patients (69% versus 7%, p<0.001, Fisher's Exact test). For scalp-treated patients, the difference between the treatment groups was not statistically significant but was numerically in favor of PEP005 Gel (23% versus 4%, p=0.099, Fisher's Exact test).

The median percent reduction in the number of AK lesions compared to baseline overall (face and scalp combined) was substantially greater for the PEP005 Gel group (83%) versus 0% in the vehicle group. For patients treated on the face, the median reduction was 83% for the PEP005 Gel group versus 0% in the vehicle group. For patients treated on the scalp, the median reduction was 49% for the PEP005 Gel group versus 25% in the vehicle group.

In the subgroup analyses, the complete clearance rate for each treatment group was analyzed by geographic region (US or AUS), gender, age group (<65 or ≥65 years), baseline AK lesion count (4, 5, 6 or 7, 8), skin type (Fitzpatrick I/II or III/IV/V/VI), and analysis site. Findings showed a higher complete clearance rate for PEP005 Gel-treated patients compared to vehicle patients in each category; the only category that did not show statistical significance was the geographic region of Australia.
Patient reported outcomes included the TSQM and the Skindex-16 Dermatology Survey. Statistically significant, higher mean patient global satisfaction scores, measured by the TSQM, were seen in the PEP005 Gel group compared to the vehicle gel group (p < 0.001). For the Skindex-16 Dermatology Survey, a statistically significant difference was seen with PEP005-treated patients less bothered by each of the three domains (symptoms, emotions, and functioning) compared to vehicle gel; the positive effect was seen at Day 29 (p < 0.001, each domain) and continued at Day 57 (p < 0.001, each domain).

**Safety:**
PEP005 Gel, 0.015% was, in general, well tolerated when applied once daily for three consecutive days.

Compliance to the treatment regimen was 96% for the PEP005 Gel group and 100% for the vehicle gel group (ITT population).

No deaths occurred during the study. Four patients (two in each treatment group) experienced seven SAEs. In the PEP005 Gel group, one patient had Campylobacter infection and a small bowel obstruction and another patient had a meniscus tear and hypoxia. In the vehicle gel group, one patient had a multiple trauma injury and a pulmonary embolism and one patient had a vascular pseudoaneurysm. None of these events were considered related to study medication. Three patients discontinued the study or study medication due to adverse events. One PEP005 Gel patient discontinued study medication due to application site pain; this event was severe, definitely related, and resolved without sequelae. Two patients discontinued the study after applying all three doses of study medication. One PEP005 Gel patient experienced application site burning, eye pain, eye burning, and periorbital edema; all events were severe, the application site pain was considered definitely related to study medication and the other events were considered to be probably related to study medication. One vehicle patient experienced multiple trauma (explained above as an SAE) which resulted in study discontinuation.

Application site reactions were the most common treatment-related AEs reported for the PEP005 Gel patients, with pain and pruritus reported as the most frequent application site events. Application site infection occurred in five PEP005 Gel patients, all cases were first documented at Day 4, were considered mild in severity, and typically resolved within a week or two. Bleeding and discharge at the application site occurred in only 1 patient each. Other treatment-related events included headache, eye pain, conjunctivitis, and eyelid/periorbital edema, adjacent to the treatment area. The majority of treatment-related adverse events were mild or moderate in severity. Only three PEP005 Gel-treated patients (2%) experienced treatment-related events that were considered severe. In all cases, the treatment-related events resolved without sequelae.

The most common LSRs were erythema (100% for PEP005, 63% for vehicle), flaking/scaling (99% for PEP005, 73% for vehicle) and crusting (86% for PEP005, 29% for vehicle). Grade 4 LSRs were observed in approximately 30% of the PEP005 Gel group. Mean composite LSR scores (maximum score of 24) peaked at Day 4 for the PEP005 Gel group (9.47) and at Day 8 for the vehicle gel group (1.42); by Day 29, scores were lower than baseline levels. All LSRs resolved without sequelae.

Hypopigmentation and hyperpigmentation assessments remained unchanged from baseline at Day 57 in the majority of patients. Four patients (three PEP005 patients and one vehicle patient) had hypopigmentation or hyperpigmentation at Day 57 which was not present at baseline. One PEP005 patient with hypopigmentation required followup and was deemed clinically stable by the investigator on Day 80. No treatment emergent scarring was observed. No patients had confirmed abnormal proliferation within the treatment area during the study. No clinically meaningful differences were observed between the treatment groups when actual and change from baseline values were assessed for hematology and serum chemistry tests, vital signs, and interval-valued ECG parameters. Results of physical examinations showed no clinically relevant findings.
Conclusion:
The following conclusions are based on the results of this study:

- The treatment regimen of PEP005 Gel, 0.015% applied daily for three consecutive days was shown to be effective in completely clearing a contiguous 25 cm² treatment area of AK lesions on the head (face and scalp).
- Other efficacy endpoints provided confirmation of the treatment effect. The partial clearance rate was significantly higher in patients treated with PEP005 Gel and the median percent reduction from baseline in the number of AK lesions was substantially greater.
- Patient compliance with the treatment regimen was high; 96% of PEP005 Gel patients completed the full course of therapy.
- PEP005 Gel, 0.015%, in general, appeared to be safe and well-tolerated when used to treat AK lesions on the face and scalp. No serious adverse events were considered treatment-related. All treatment-related application site adverse events and local skin responses resolved without sequelae.

Final Report Date: 8 September 2010