Sponsor: Peplin Operations Pty Ltd

Name of Finished Product: PEP005 (ingenol mebutate) Gel

Name of Active Ingredient: Ingenol Mebutate

Title:
A multi-center, randomized, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) Gel, 0.05% in patients with actinic keratoses on non-head locations (REGION-I)

Investigators and Sites: Multicenter in the United States and Australia (refer to Appendix 16.1.4.1)

Publications: None

Study Period:
First patient randomized: 05 September 2008
Last patient completed Day 57: 23 February 2009

Phase of Development: 3

Objectives:
To evaluate the efficacy and safety of PEP005 Gel, 0.05% compared to vehicle gel, when administered once daily for two consecutive days (Day 1 and Day 2) to a 25 cm² contiguous actinic keratosis (AK) treatment area on non-head locations.

Methodology:
This was a multicenter, randomized, double-blind, parallel group, vehicle-controlled study. Eligible patients were randomized to receive PEP005 Gel, 0.05% or vehicle gel once daily for two consecutive days (Days 1 and 2). Study medication was patient-applied at home. Safety assessments were performed during study visits on Days 3, 8, 15, 29, and 57 following treatment. Efficacy assessments were performed at baseline (Day 1 predose) and Day 57 (end of study). Patient-reported treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication (TSQM) was assessed on Day 57, and skin-related quality of life using the Skindex-16 Dermatological Survey was assessed on Days 1, 8, 29, and 57. Patients completed the study on Day 57.

Poststudy followup visits were required every 7 to 28 days for all patients with unresolved, treatment related adverse events (AEs) or local skin responses (LSRs) at Day 57 (if LSR grade was greater than baseline grade). These patients were to be followed until the events resolved or were assessed as clinically stable. Additionally, patients with treatment related pigmentation changes (hypo/hyper) or scarring greater than that present at baseline were required to undergo further poststudy followup every 28 days until resolution of the event or for a period of 6 months postbaseline (an additional 4 visits) unless deemed clinically insignificant.

Number of Patients (Planned and Analyzed):
Planned: approximately 250 patients (125 per treatment group)
Analyzed:
Intent-to-treat (randomized): 255 patients (126 to PEP005 Gel, 0.05% and 129 to vehicle gel)
Safety: 254 patients (125 PEP005 Gel, 0.05%; 129 vehicle gel)

Diagnosis and Main Criteria for Inclusion:
Male or female patients at least 18 years of age with 4 to 8 clinically typical, visible, and discrete AK lesions within a contiguous 25 cm² treatment area on the trunk and extremities (i.e., non-head locations).
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**Test Product and Reference Therapy, Dose, Mode of Administration and Batch Nos.:**
Test product: PEP005 Gel, 0.05% (Batch No. AGK-C).
Reference therapy: Vehicle gel (Batch No. ZMAB-C).

Study medication (PEP005 Gel, 0.05% or vehicle gel) was packaged individually for each patient in a study medication kit containing two unit-dose tubes. Study medication was applied topically to the selected treatment area by the patient, at home, once daily on study Days 1 and 2.

**Duration of Treatment:**
Two consecutive days (Days 1 and 2)

**Randomization Scheme:**
Patients were randomized in a 1:1 ratio to study medication (PEP005 Gel, 0.05% or vehicle gel) using a central Interactive Voice Response/Interactive Web Response (IVR/IWR) system. Randomization was stratified by study site and also by anatomical location of the selected treatment area. A dynamic randomization scheme was used to obtain an approximate 1:1 ratio between treatment groups. Hierarchy levels were overall balance, balance within each anatomical location, and balance within each study site. A biased-coin approach was used when imbalance at a given level exceeded the specified threshold. The specified threshold level (i.e., difference between the number of randomized patients in each treatment group) for triggering the biased-coin approach was 4 for overall balance, 2 for balance within each anatomical location, and 2 for balance within each study site.

**Criteria for Evaluation:**

**Efficacy:**

*Primary efficacy endpoint:*
Complete clearance rate of AK lesions at Day 57, defined as the proportion of patients with no clinically visible AK lesions in the selected treatment area at Day 57.

*Secondary efficacy endpoint:*
Partial clearance rate of AK lesions at Day 57, defined as the proportion of patients at Day 57 with a 75% or greater reduction in the number of AK lesions identified at baseline in the selected treatment area.

*Additional efficacy endpoint:*
Percent change from baseline to Day 57 in the total number of AK lesions.

**Exploratory:**
Patient-reported outcomes, including the TSQM at Day 57 and the Skindex-16 Dermatological Survey at baseline and Days 8, 29, and 57.

**Safety:**
- Incidence of AEs, serious adverse events (SAEs), and AEs leading to discontinuation of study medication.
- Incidence and grade of LSRs.
- Incidence and grade pigmentation and scarring.
- Clinical laboratory tests, vital signs, physical examinations, and electrocardiogram (ECG) findings.

**Statistical Methods:**
All statistical tests were two-sided with a significance level of $\alpha = 0.05$, unless specified otherwise. Data were summarized using descriptive statistics (number of patients [n], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and frequency and percentages for discrete variables. Missing values were imputed using the last observation carried forward (LOCF) method, unless specified otherwise.
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### Efficacy

Complete clearance rates were calculated using observed rates and using weighted estimates based on the Cochran-Mantel-Haenszel (CMH) test statistic stratifying on anatomical location. Treatment groups were compared using the CMH test. A logistic analysis of variance (ANOVA) with treatment, anatomical location, and country as factors was also used to test for treatment effect. Partial clearance rates were calculated and the treatment groups were compared using the same methods as those used for the primary efficacy endpoint. Percent reduction from baseline in AK lesions at Day 57 was summarized using descriptive statistics. For exploratory purposes, summaries of complete clearance, partial clearance, and percent reduction from baseline in AK lesions at Day 57 were presented by anatomical location. Efficacy analyses were based primarily on the intent-to-treat (ITT) population, which includes all patients randomized into the study. In the ITT population, patients were counted in the treatment group to which they were randomized, regardless of receiving any dose of study medication.

### Patient-Reported Outcomes

Treatment Satisfaction Questionnaire for Medication transformed scores at Day 57 and the Skindex-16 Dermatological Survey transformed scores at each scheduled visit were summarized by treatment group. The transformed scores were treated as a continuous variable and analyzed using ANOVA with treatment, anatomical location, and study site as factors to test for treatment effect.

### Safety

The safety analysis was based on the safety population, which included 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. Treatment effect for safety endpoints was explored by inspection of observed means or frequency rates between treatment groups. Treatment groups were compared in terms of the incidence of AEs using the CMH test. ANOVA was used to compare the treatment groups in terms of change in LSR grade.

### Summary of Results:

**Efficacy:**

The observed complete clearance rate at Day 57 (ITT LOCF) overall was statistically significantly higher in the PEP005 Gel, 0.05% group (28%) than the vehicle group (5%) (p < 0.0001). Sensitivity analyses, including a multiple imputation method for handling missing data and analyses based on evaluable and PP populations, all demonstrated a statistically significantly higher complete clearance rate in the PEP005 Gel, 0.05% group than in the vehicle group (p < 0.0001 for all comparisons). Observed complete clearance rates by anatomical location in the PEP005 Gel, 0.05% group versus vehicle group, respectively, were as follows: arm, 26% (22/84) vs. 5% (4/82); back of hand, 16% (4/25) vs. 0 (0/29); chest, 89% (8/9) vs. 13% (1/8); and other (shoulder, back, and leg), 13% (1/8) vs. 10% (1/10).

The results of the analysis of the secondary efficacy endpoint, partial clearance (≥75% reduction) in AK lesions at Day 57, support the results of the primary efficacy analysis. The observed partial clearance rate at Day 57 overall in the PEP005 Gel, 0.05% group was 44% (56/126) versus 7% (9/129) in the vehicle group (p < 0.0001). Observed partial clearance rates by anatomical location in the PEP005 Gel, 0.05% group versus vehicle group, respectively, were as follows: arm, 48% (40/84) vs. 9% (7/82); back of hand, 24% (6/25) vs. 0 (0/29); chest, 89% (8/9) vs. 13% (1/8); and other (shoulder, back, and leg), 25% (2/8) vs. 10% (1/10).

Treatment with PEP005 Gel, 0.05% resulted in a greater reduction in AK lesion count than treatment with vehicle. Median percent reduction from baseline in lesion count at Day 57 overall in the PEP005 Gel, 0.05% group was 69% versus 0 (zero) in the vehicle group. Median percent reduction in AK lesion count by anatomical location in the PEP005 Gel, 0.05% group versus vehicle group, respectively, was as follows: arm, 75% vs. 0; back of hand, 50% vs. 0; chest, 100% vs. 0; and other (shoulder, back, and leg), 57% vs. 0.
### Individual Study Table Referring to Part of the Dossier

<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>
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</table>

### Synopsis

**PEP005 (ingenol mebutate) Gel**

**Sponsor:**
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**Individual Study Table Referring to Part of the Dossier**

**Volume:**

**Page:**

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Patient-reported Global Satisfaction mean score at Day 57, as measured by the TSQM, was statistically significantly higher in the PEP005 Gel, 0.05% group (71.3) relative to the vehicle group (47.8) (p < 0.0001), indicating a significantly higher level of overall satisfaction with PEP005 Gel, 0.05% relative to vehicle. For the Skindex-16 Dermatology Survey, mean scores for all three domain scores (Symptoms, Emotions, and Functioning) at Day 57 were decreased from baseline both in the PEP005 Gel, 0.05% group and the vehicle group, indicating improvement in patient concern regarding their skin condition in both treatment groups. There were no statistically significant differences between treatment groups in any of the three domains at Day 57.

### Safety:

PEP005 Gel, 0.05% applied topically once daily for two consecutive days was well tolerated in this study. In the PEP005 Gel, 0.05% group, 98% of patients applied study medication on both days of dosing. Two patients did not apply the second dose due to application site reactions (application site pain [AE] in one patient; erythema and erosion [LSRs] in one patient).

The most common treatment related AEs were general disorders and administration site conditions relating to the application site (5 patients in the PEP005 Gel, 0.05% group; 0 patients in the vehicle group). All application site AEs were mild or moderate in intensity. Three patients had treatment related AEs other than application site reactions. Patient 63/003 in the PEP005 Gel, 0.05% group (treatment area, left leg) had vesiculation (blister) and erythema on the right leg at the point of contact with the treatment area. Patient 64/004 in the PEP005 Gel, 0.05% group (treatment area, left arm) had dermatitis on the right cheek due to cross-contamination with the treatment area. Patient 70/001 in the vehicle group developed a staphylococcal skin infection in the treatment area (chest) confirmed by a pustule swab culture. Four patients had SAEs, 1 patient in the PEP005 Gel, 0.05% group and 3 patients in the vehicle group. All SAEs were assessed by the investigator as not related to study medication. One patient in the PEP005 Gel, 0.05% group discontinued study medication due to an AE, i.e., application site pain (treatment area, chest) after the Day 1 dose that precluded further application on Day 2. A second patient in the PEP005 Gel, 0.05% group discontinued study medication due to LSRs, i.e., erythema and erosion (treatment area, arm) after the Day 1 dose that precluded further application on Day 2. No AEs leading to discontinuation of the study (2 patients in the PEP005 Gel, 0.05% group and 1 patient in the vehicle group) were considered related to study medication. Abnormal proliferation in the treatment area was reported for one patient in the PEP005 Gel, 0.05% group. Biopsy of the treatment area (thigh) revealed chronic eczematous dermatitis associated with focal AK, which was assessed by the investigator as mild in intensity and probably related to study medication. The patient completed the post study followup on Day 146. Outcome of the event, which was ongoing at last contact, was listed as "little or no change."

The treatment area was assessed for LSRs (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration) at baseline (Day 1 predose) and each subsequent study visit. The mean LSR composite score (maximum score of 24) for the PEP005 Gel, 0.05% was 1.0 at baseline, peaked at 5.4 at Day 8, and returned to below baseline (0.8) at Day 57. The mean LSR composite score in the vehicle group did not change substantially across study visits. In the PEP005 Gel, 0.05% group, the most frequently reported LSRs were erythema (92 of patients at Day 8) and flaking/scaling (90% of patients at Day 8). Erythema, flaking/scaling, crusting, erosion/ulceration peaked at Day 8; swelling and vesiculation/pustulation peaked at Day 3. By Day 57, patient frequency of most LSRs (erythema, flaking/scaling, crusting, and vesiculation/pustulation) had returned to or was below baseline level; patient frequency of swelling and erosion/ulceration was reduced substantially from peak level and had returned to close to baseline level. In the vehicle group, patient frequencies of LSRs were generally unchanged over time. The difference between PEP005 Gel, 0.05% and vehicle treatment in patient frequency of LSRs was greatest at Day 8. Thirteen patients in the PEP005 Gel, 0.05% group had one or more Grade 4 LSRs during the study. For all except 2 patients, Grade 4 LSRs had returned to or near baseline grade by Day 57. Three patients, 1 patient in the PEP005 Gel, 0.05% group and 2 patients in the vehicle group, had one or more LSRs that required poststudy followup. All of these LSRs returned to or near baseline grade during the follow-up period.
For the majority (>95%) of patients, pigmentation (hyper and hypo) and scarring remained unchanged during the study (baseline [Day 1] to Day 57). Four (3%) patients in the PEP005 Gel, 0.05% group experienced greater hypopigmentation and/or hyperpigmentation relative to baseline. No patients in the PEP005 Gel, 0.05% group experienced scarring greater than what was observed at baseline. One patient in the vehicle group experienced greater hyperpigmentation and scarring (atrophic) relative to baseline. Two patients with hyperpigmentation in the PEP005 Gel, 0.05% group required poststudy followup. At completion of the followup period, hyperpigmentation had resolved in one patient and remained at Grade 2 in the other patient.

Changes from baseline in clinical laboratory tests and vital signs were unremarkable and similar between the PEP005 Gel, 0.05% and vehicle treatment groups. There were no apparent differences between treatment groups in ECG findings and no mean QT/QTc prolongations were observed.

Conclusion:

- PEP005 Gel, 0.05% applied topically once daily for two consecutive days was shown to be safe and efficacious for the treatment of AK lesions on non-head locations (trunk and extremities).
- Nearly all patients (98% in the PEP005 Gel, 0.05% group) were compliant with the treatment regimen, i.e., applied study medication on both days of dosing.
- Complete clearance rate at Day 57 was significantly higher in the PEP005 Gel, 0.05% group relative to the vehicle group.
- Other efficacy variables support the results of the primary efficacy endpoint. The partial clearance rate at Day 57 was significantly higher in the PEP005 Gel, 0.05% group relative to the vehicle group. Median percent reduction from baseline in lesion count at Day 57 was substantially reduced in the PEP005 Gel, 0.05% group relative to the vehicle groups.
- The most common treatment related AEs were application site reactions. There were no deaths and no treatment related SAEs. All treatment related application site AEs and LSRs resolved without sequelae.

Final Report Date: 16 September 2010