2 SYNOPSIS

Sponsor:
Peplin Operations Pty Ltd

Name of Finished Product:
PEP005 (ingenol mebutate) Gel

Name of Active Ingredient:
Ingenol Mebutate

Title:
A multicenter, open-label study to examine the safety and toleration of 0.05% PEP005 Topical Gel in patients with actinic keratoses on the dorsum of the hand

Investigators and Sites: Multicenter in the US. Description of investigators and sites has been provided in Appendix 16.1.4

Publications: None

Study Period:
First patient enrolled: October 11, 2007
Last patient completed Day 57: December 18, 2007

Phase of Development: 2

Objectives:
Primary Objective:
To examine the safety and toleration of PEP005 Gel, 0.05%, administered on two consecutive days, to a 25 cm² contiguous actinic keratosis (AK) treatment area on the dorsum of a single hand as determined by:
- incidence of adverse events (AEs) and serious adverse events (SAEs); and
- local skin responses (LSRs).

Secondary Objective:
To examine the efficacy of PEP005 Gel, 0.05%, administered on two consecutive days, to a 25 cm² contiguous AK treatment area on the dorsum of a single hand as determined by the:
- complete clearance rate: the proportion of patients at the Day 57 post-treatment visit with no clinically visible AK lesions in the selected AK treatment area;
- partial clearance rate: the proportion of patients at the Day 57 post-treatment visit with a 75% or greater reduction in the number of AK lesions identified at baseline in the selected AK treatment area; and
- baseline clearance rate: the proportion of patients at the Day 57 post-treatment visit with a 100% reduction in the number of AK lesions identified at baseline in the selected AK treatment area.

Methodology:
This was a Phase 2, multicenter, open-label study to evaluate the safety and tolerability of PEP005 Gel, 0.05%, administered once daily on two consecutive days to patients with AK lesions on the dorsum of one hand.

Patients were screened for study eligibility from Day -14 through Day -3. All eligible patients had study medication applied on Days 1 and 2. Patients were assessed for safety, tolerability, and efficacy on Days 2, 8, 15, 29, and 57. Additional post-Day 57 follow-up visits were planned, if clinically indicated.

Number of Patients (Planned and Analyzed):
Approximately 12 patients were planned for enrollment. A total of 12 patients were enrolled, 11 of which were treated with study medication and analyzed.

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**Diagnosis and Main Criteria for Inclusion:**
Male and/or postmenopausal female patients at least 18 years of age with 4–8 clinically typical, visible, and discrete AK lesions within a contiguous 25 cm² treatment area on the dorsum of one hand. One lot of study medication, , was used in this study.

**Dosage, Administration, and Duration of Treatment:**
All patients received PEP005 Gel, 0.05%, once daily for two consecutive days (study Days 1 and 2). The study medication was applied topically to the selected AK treatment area by a board-certified dermatologist.

**Randomization Scheme:**
Not applicable, this was an open-label study.

**Statistical Methods and Criteria for Evaluation:**
This was an open-label, nonrandomized study with no formal hypothesis testing. The analysis was primarily descriptive in nature. Due to the small number of patients at each site, data from all sites were pooled.

Safety and tolerability assessments included AEs, SAEs, and LSRs. AEs and SAEs were summarized by the number and percentage of patients for each event. LSRs were assessed using a 4-point grading scale for each LSR. A composite score representing the sum of the individual LSRs was calculated for each study visit and the results were summarized using descriptive statistics. Other safety assessments included clinical laboratory evaluations, vital signs data, and physical examination findings, all of which were summarized using descriptive statistics.

Primary efficacy variables included complete clearance, partial clearance, and baseline clearance rates. The number and percentage of patients with lesion clearance and 95% confidence intervals (determined using the binomial approximation to the normal distribution) were calculated for each study visit. Additional efficacy variables included the overall clearance rate by number of doses received, the median percentage reduction in AK lesions, and the number and percentage of patients with subclinical AK lesions, visible AK lesions, and remaining baseline AK lesions within the treatment area. Additional efficacy variables were summarized using descriptive statistics.

An interim analysis was conducted on all patients once they had completed their Day 29 scheduled visit (including patients who were withdrawn prematurely). The interim analysis was performed on selected safety, tolerability, and efficacy data. No p-value adjustment was required and the interim analysis was not expected to bias or influence the integrity of the final analysis.

**Summary of Results:**

**Safety results**
All patients received two consecutive once-daily doses of PEP005 Gel, 0.05%, as planned. No deaths or discontinuations occurred during the study. There was one SAE, which the investigator deemed unrelated to study medication; this was a squamous cell carcinoma in situ (SCCIS) on the chest in a patient with a prior history of SCC, and was considered to be resolved by Day 57.

The most common AE class was 'general disorders and administration-site conditions' (27.3%; 3/11 patients). All AEs were mild or moderate in intensity, except for one case of severe cystitis that was unrelated to treatment. All but three AEs resolved by Day 57; these three AEs occurred in the same patient and were considered to be unrelated to study treatment.

Three patients experienced a total of seven treatment-related AEs, all of which occurred in the treatment area. This total included four reports of application-site reactions, and one report each of hypersensitivity, irritation, and paresthesia in the treatment area. All treatment-related AEs were mild in intensity and all but one resolved within 1 day; the exception was application-site hypersensitivity, which resolved within 6 days.

The mean composite LSR score was 1.5 at baseline, peaked on Day 8 with a score of 4.5, and returned to near pretreatment levels (1.6) at Day 29. The maximum composite LSR score reported in the study was 8, from a maximum possible score of 32.

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<tbody>
<tr>
<td>Name of Finished Product: PEP005 (ingenol mebutate) Gel</td>
<td>Volume:</td>
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<tr>
<td>Name of Active Ingredient: Ingenol Mebutate</td>
<td>Page:</td>
<td></td>
</tr>
</tbody>
</table>

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Page 4
Throughout the study, the most common LSRs were flaking/scaling and erythema, followed by crusting. Flaking/scaling was reported in 63.6% (7/11) of patients at baseline, and occurred in all patients on Days 8 and 15; the incidence of flaking/scaling improved to below baseline levels by Day 57. Erythema was present in 36.4% (4/11) of patients prior to treatment, and in all patients following dosing on Day 2. At Day 57, erythema was present in five patients (45.5%; 5/11). Only one patient (9.1%; 1/11) had signs of crusting at baseline. The incidence of crusting peaked at 72.7% (8/11 patients) on Day 8, and equaled baseline levels at Day 57. Swelling was observed only on Day 2, in two patients. The combined incidence of hyperpigmentation and hypopigmentation remained unchanged throughout the study, and no erosion/ulceration, scarring, or vesiculation/pustulation was reported at any time.

There were no Grade 4 LSRs, and Grade 3 post-dose LSRs were limited to flaking/scaling and erythema in 18.2% (2/11) of patients each. Grade 2 flaking/scaling occurred post-dose in 54.5% (6/11) of patients. For the remaining LSRs, the highest recorded post-dose grade was either Grade 0 (absent) or Grade 1 in the majority of patients: 100% (11/11) for erosion/ulceration, scarring, and vesiculation/pustulation, 90.9% (10/11) for pigmentation abnormalities and swelling, 63.6% (7/11) for erythema, and 54.5% (6/11) for crusting.

By Day 57, most LSRs were unchanged from baseline or had improved. Two patients had a total of four Grade 1 LSRs at Day 57 that were not present at baseline. Overall, the highest LSR grade at Day 57 was pre-existing Grade 2 hyperpigmentation in one patient.

No abnormal proliferation was reported in the treatment area, and no patients had clinically significant laboratory abnormalities, changes in vital signs or physical examination findings.

Efficacy results

Efficacy was a secondary objective in this study.

At Day 57, the complete clearance rate was 27.3% (3/11 patients), and the partial clearance rate was 45.5% (5/11 patients). The complete clearance rate was highest on Day 15 (45.5%; 5/11 patients), while the partial clearance rate was highest on Day 29 (63.6%; 7/11 patients).

The median percentage reduction in AK lesion count from baseline to Day 57 ranged from an increase of 12.5% to a decrease of 100.0%, with an overall median reduction of 66.7%. The median lesion count in the treatment area decreased from 6.0 on Day 2 to 0.0 on Day 15, increasing to 2.0 by Day 57. However, AK lesions were unable to be determined/assessed in a percentage of patients on Days 8 (5/11; 45.5%) and 15 (4/11; 36.4%).

Treatment-emergent subclinical lesions were identified in three patients (27.3%) on Day 57, based on a comparison of the total number of lesions at Day 57 with the lesions identified at baseline.

Conclusion:

The results of this study demonstrate that PEP005 Gel, 0.05%, is safe and well tolerated when applied once daily on two consecutive days to a 25 cm² contiguous AK treatment area on the dorsum of a single hand. Although complete clearance was observed in this study, the sample size was small and further study in a larger patient population is needed to confirm the response rates in this treatment area.

Final Report Date: 12 August 2009