2 SYNOPSIS

Sponsor: Peplin Operations Pty Ltd

Name of Finished Product: PEP005 (ingenol mebutate) Gel

Name of Active Ingredient: Ingenol Mebutate

Title: A 12-month, long-term follow-up study of patients with actinic keratosis on the head (face or scalp) who have completed Day 57 in studies PEP005-016 or PEP005-025 (REGION IIa and IIb)

Investigators and Sites: 38 centers in the United States and 4 centers in Australia

Publications: None

Study Period:
First patient enrolled: 29 July 2009
Last patient completed: 16 September 2010

Phase of Development: 3

Objectives:
To summarize treatment area recurrence of actinic keratosis (AK) lesions, in the selected treatment area, during a 12-month followup period for patients who achieved complete clearance of AKs at Day 57 in studies PEP005-016 and PEP005-025.

To summarize long-term safety data, in the selected treatment area over a 12-month followup period for patients who completed Day 57 in studies PEP005-016 and PEP005-025.

Methodology:
This was a prospective, longitudinal, observational study in patients who achieved complete clearance at Day 57 in studies PEP005-016 and PEP005-025. No study medication was administered during PEP005-030.

The original protocol dated July 1, 2009, allowed entry of patients who completed the Day 57 visit in studies PEP005-016 and PEP005-025. With implementation of Amendment #1, dated September 28, 2009, eligibility was restricted to only those patients who achieved complete clearance at Day 57. Consequently, enrolled patients who had not achieved complete clearance at Day 57 were terminated from the study at the next regularly scheduled PEP005-030 study visit, or sooner if feasible.

Following enrollment (at Day 57 or within 4 weeks after Day 57 of studies PEP005-016 and PEP005-025), patients were to return to the clinic for followup visits at 3, 6, 9, and 12 months after the Day 57 visit in the previous study.

Information was collected for all patients on adverse events (AEs) in the selected treatment area and concomitant therapies (medications and procedures) specific to the selected treatment area. AK lesions in the selected treatment area were counted at each visit. Information regarding intercurrent disorders, therapeutics that could have resulted in immunosuppression, and treatment with agents known to alter AK were collected.

Number of Patients (Planned and Analyzed):
Planned: Approximately 160 patients
Analyzed: A total of 117 patients who had demonstrated complete clearance of AK lesions in either study PEP005-016 or PEP005-025 were enrolled in this long-term followup study. Of these 117 patients, 108 had received 0.015% PEP005 Gel and 9 had received vehicle in the previous study.
Name of Finished Product:
PEP005 (ingenol mebutate) Gel

Name of Active Ingredient:
Ingenol Mebutate

Diagnosis and Main Criteria for Inclusion:
Patients had to achieve complete clearance of AK lesions at Day 57 in either study PEP005-016 or PEP005-025.

Test Product and Reference Therapy, Dose, Mode of Administration and Lots:
Test product: Not applicable; no study medication was administered during this study.
Reference therapy: Not applicable

Duration of Study:
It was estimated that it would take 15 months to complete this study from the first patient enrolled to the last patient followup visit.

Randomization Scheme:
Not applicable

Criteria for Evaluation:

Efficacy:
Number of AK lesions in the selected treatment area. Recurrence was defined as any identified AK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase 3 study. Concomitant therapies (medications and procedures) for treatment of AK lesions in the selected treatment area.

Safety:
AEs in the selected treatment area.

Statistical Methods:
The statistical evaluations were planned to be performed after the 6-month followup visit and again after the 12-month followup visit (i.e., completion of the study). This clinical study report is based on data obtained through the 12-month followup visit.

Three analysis populations were defined: (1) the ‘All Patients Enrolled’ population included all patients who provided informed consent for participation in the study; (2) the ‘CC57’ population included all patients enrolled who showed complete clearance of AK lesions in the selected treatment area at the Day 57 visit in study PEP005-016 or PEP005-025; and (3) the ‘Non-CC57’ population included all patients enrolled who did not show complete clearance of AK lesions in the selected treatment area at the Day 57 visit in the previous study. Patients were classified into treatment groups according to the treatment received in the previous study.

Efficacy: For the CC57 population, AK recurrence was summarized using Kaplan-Meier methods. All event times were imputed to their target study day prior to performing the calculations. The recurrence rate was estimated by the Kaplan-Meier “failure” estimate at the target study day expressed as a percentage. The estimates, along with 95% confidence intervals, were calculated at Days 91, 183, 274, and 365. The time to recurrence was also summarized. The recurrence rate at Day 365 (12 months) was summarized for the subgroups of treatment location, geographic region, Fitzpatrick skin type, gender, age group, and baseline lesion count. The number of AK lesions in the treatment area was summarized at each visit.

Safety: For the CC57 population, the incidence rate of AEs was summarized as the number and percentage of patients with one or more episodes of an AE classified using the MedDRA (Version 11.0) preferred term and system-organ class. An overall summary of AEs was presented and included the number and percentage of patients with any AE, any serious AE (SAE), any fatal AE, any severe AE, and any AE resulting in discontinuation of study. The incidence of all AEs by preferred term regardless of the relationship to previous study treatment was summarized for each treatment group. Patients with SAEs, fatal AEs, severe AEs, and AEs leading to study
discontinuation were presented in data listings. AE data for the Non-CC57 population were presented in data listings.

**Summary of Results:**

**Efficacy:** At 12 months of followup, 53.9% of patients who had been treated with PEP005 Gel in the previous Phase 3 studies (N=108), had at least one new or recurrent AK lesion within the selected treatment area. The estimated median time to lesion recurrence was 365 days. Based on the number of lesions observed within the treatment area during 12 months of followup relative to the number of lesions at baseline (determined prior to treatment with PEP005 Gel in the Phase 3 studies), the mean lesion-based recurrence rate was 12.8%.

At 12 months of followup, 72.2% of vehicle-treated patients (N=9) had a new or recurrent AK lesion, with a median time to recurrence of 183 days. For this group of patients, the mean lesion-based recurrence rate at 12 months was 16.3%.

**Safety:** Over the 12-month followup study, only 1 AE in the selected treatment area (mild sunburn, considered unrelated to study drug) was reported.

**Conclusion:**

During 12 months of followup, 53.9% of patients had at least one new or recurrent AK lesion within the area on the face or scalp that had been treated with PEP005 Gel, 0.015% in study PEP005-016 or PEP005-025; the median time to recurrence was 365 days. Relative to the total number of AK lesions observed prior to treatment in either study PEP005-016 or PEP005-025, the lesion recurrence rate at 12 months of long-term followup was 12.8%. With only one reported AE of mild, unrelated sunburn, there was no safety concern in the selected treatment area.

**Final Report Date:** 28 March 2011