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 non-head locations (trunk and extremities) who have completed Day 57 in study PEP005-028

**Investigators and Sites:**
15 centers in the United States

**Publications:**
None

**Study Period:**
First patient enrolled: 09 September 2009
Last patient completed: 11 October 2010

**Phase of Development:**
3

**Objectives:**
To summarize treatment area recurrences of actinic keratosis (AK) lesions, in the selected treatment area during a 12-month followup period for patients with complete clearance, who completed Day 57 in study PEP005-028.

To summarize long-term safety data, in selected treatment area over a 12-month followup period for patients with complete clearance, who have completed Day 57 in study PEP005-028.

**Methodology:**
This was a prospective, longitudinal, observational study in patients who achieved complete clearance at Day 57 in study PEP005-028. No study medication was administered during PEP005-032.

Patients were enrolled at Day 57 (or within 4 weeks after Day 57) of the previous study. 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. The number of AK lesions in the selected treatment area was counted at each visit. Information regarding intercurrent disorders, therapeutics that could have resulted in immunosuppression, and treatment with agents known to alter actinic keratosis was collected.

**Number of Patients (Planned and Analyzed):**
Planned: Approximately 40 patients
Analyzed: A total of 43 patients were enrolled (38 received PEP005 Gel 0.05% and 5 received vehicle gel in the previous study [PEP005-028]).
Diagnosis and Main Criteria for Inclusion:
Patients had to achieve complete clearance of AK lesions at Day 57 in the previous study, PEP005-028.

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 described below 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).
Two analysis populations were defined as follows: (1) the ‘All Patients Enrolled’ population included all patients who signed an informed consent for participation in the study within 4 weeks of the Day 57 visit in the previous study (PEP005-028) and (2) the ‘CC57’ population included all patients enrolled who showed complete clearance of AK lesions in the selected treatment area at Day 57 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. Time to recurrence was also summarized. The recurrence rate at Day 365 was summarized for subgroups of interest. 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 the 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.

Summary of Results:

Efficacy: At 12 months of followup, 50% of patients treated with PEP005 Gel, 0.05% in study PEP005-028 (N=38) had at least one new or recurrent AK lesion within the selected treatment area. The estimated median time to recurrence was > 183 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 14.9%.

At 12 months of followup, 80% of patients treated with vehicle gel in the previous study (N=5) had a new or recurrent AK lesion, with a median time to recurrence of 183 days, and the mean lesion-based recurrence rate at 12 months was 19.2%.

Safety: Over the 12 months of followup, only 1 AE in the selected treatment area (mild rash, considered unrelated to study drug) was reported among the 38 subjects treated with PEP005 Gel, 0.05% in study PEP005-028; no other AEs or safety concerns were reported.

Conclusion:

During 12 months of followup, 50% of patients had at least one new or recurrent AK lesion within the treatment area on the trunk or extremities that had been treated with PEP005 Gel, 0.05% in study PEP005-028; the median time to recurrence was > 183 days. Relative to the total number of AK lesions observed prior to treatment in study PEP005-028, the lesion-based recurrence rate at 12 months of long-term followup was 14.9%. With only one reported AE of mild, unrelated rash, there was no safety concern in the selected treatment area.

Final Report Date: 28 March 2011