2 SYNOPSIS

Sponsor: Peplin Operations Pty Ltd

Individual Study Table Referring to Part of the Dossier
Volume: Page: (For National Authority Use only)

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 areas (trunk and extremities) who have completed Day 57 in study PEP005-020

Investigators and Sites: 8 centers in the United States and 3 centers in Australia

Publications: None

Study Period:
First patient enrolled: 29 July 2009
Last patient completed: 14 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 with complete clearance who completed Day 57 in study PEP005-020.
To summarize long-term safety data, in selected treatment area over a 12-month followup period for patients who completed Day 57 in study PEP005-020.

Methodology:
This was a prospective, longitudinal, observational study in patients who achieved complete clearance at Day 57 in study PEP005-020. No study medication was administered during PEP005-031. The original protocol dated July 1, 2009, allowed entry of patients who completed the Day 57 visit in study PEP005-020. With implementation of Amendment #1, dated September 30, 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 PEP005-031 study visit or sooner, if feasible.
Following enrollment (at Day 57 or within 4 weeks after Day 57 of study PEP005-020), patients then returned to the study 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
Number of Patients (Planned and Analyzed):
Planned: Approximately 30 patients
Analyzed: A total of 38 patients who had demonstrated complete clearance of AK lesions in study PEP005-020 were enrolled in the study.

Diagnosis and Main Criteria for Inclusion:
Patients had to achieve complete clearance of AK lesions (lesion count = 0) at Day 57 in study PEP005-020.

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 13 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) 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).
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 PEP005-020; 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.
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 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. 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, 62.5% of patients in the CC57 population treated with PEP005 Gel, 0.05% in study PEP005-020 (N=38) had at least one new or recurrent AK lesion within the selected treatment area. The estimated median time to lesion recurrence was 274 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 study), the mean lesion-based recurrence rate was 11.3%.

Safety:
Over the 12 months of followup in this observational study, only 1 AE in the selected treatment area was reported for the 38 patients in the CC57 population (haematoma of moderate severity, considered unrelated to study drug). Among the 60 patients in the Non-CC57 population (who had not shown complete clearance of AK lesions at the Day 57 visit in study PEP005-020 and who were terminated from this followup study), 1 patient had an AE (basal cell carcinoma of moderate severity, considered by the investigator as not related to study medication).

Conclusion:
During 12 months of followup, 62.5% of patients who had complete clearance of AK lesions at the Day 57 visit following treatment with 0.05% PEP005 Gel on the trunk and extremities in study PEP005-020 had a new or recurrent AK lesion within the treatment area, with a median time to recurrence of 274 days. Relative to the total number of AK lesions observed prior to treatment in study PEP005-020, the lesion recurrence rate at 12 months of long-term followup was 11.3%. Among the patients in this study, there was no safety concern in the selected
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