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, 0.015% In patients with actinic keratoses ON the head (face or scalp) (REGION-IIb)

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 June 2009
Last patient completed Day 57: 02 September 2009

Phase of Development: 3

Objectives:
To evaluate the efficacy and safety of PEP005 Gel, 0.015%, compared to vehicle gel when administered once daily for three consecutive days to a contiguous 25 cm2 area of skin on the head (face or scalp).

Methodology:
This was a multi-center, randomized, parallel group, double-blind, vehicle-controlled study. Patients were randomized to receive treatment with PEP005 Gel, 0.015%, or vehicle gel once daily for three consecutive days. Study medication was patient-applied at home on Days 1, 2 and 3. Subsequent followup visits for safety assessments were conducted on Days 4, 8, 15, 29 and 57. Efficacy assessments were conducted at baseline (Day 1 pre-dose) and on Day 57 (End of Study). Patient-reported treatment satisfaction was assessed on Day 57 and Quality of Life (QOL) assessments were conducted at baseline and on Days 8, 29 and 57. Patients completed the study on Day 57.

Poststudy followup visits were required every 7 to 28 days for all patients who had unresolved treatment related adverse events (AEs) or local skin responses (LSRs) at Day 57. Patients were to be followed until either resolution or assessed as clinically stable. Patients with unresolved hypopigmentation or hyperpigmentation and/or scarring greater than baseline were required to undergo further poststudy followup every 28 days until resolution or for a period of six months postbaseline (an additional four visits) unless deemed clinically insignificant.

Number of Patients (Planned and Analyzed):
Planned: Approximately 250 patients (125 per treatment arm) were planned for enrollment.
Analyzed: A total of 278 patients were randomized (142 to PEP005 Gel 0.015% and 136 to vehicle gel); 277 patients completed the study. All randomized patients were included in the intent-to-treat (ITT) population; 266 patients were included in the per-protocol (PP) population. The safety population included 278 patients.

Diagnosis and Main Criteria for Inclusion:
Male or female patients at least 18 years of age with four to eight clinically typical, visible and discrete actinic keratosis (AK) lesions within a contiguous 25 cm² treatment area on the head (face or scalp).

Test Product and Reference Therapy, Dose, Mode of Administration and Lots:
Test product: PEP005 Gel, 0.015% (Lot ).
Reference therapy: Vehicle gel (Lots and ).
Study medication was packaged individually for each patient in a study medication kit containing three unit-dose tubes. Each unit-dose tube contained PEP005 Gel 0.015% or vehicle gel.
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**Duration of Treatment:**
Study medication was applied topically to the selected treatment area by the patient, at home, once daily on study Days 1, 2 and 3.

**Randomization Scheme:**
Patients were randomized centrally to treatment in a 1:1 ratio through an interactive voice / web response (IVR/IWR) system. Randomization was stratified by investigational site and by the location of the treatment area (face or scalp). Enrollment was controlled so that approximately 20% of patients were treated on the scalp and approximately 80% of patients were treated on the face. The IVR/IWR system assigned a study medication kit number for each patient randomized into the study.

**Criteria for Evaluation:**

**Efficacy:**

**Primary Endpoint:**
Complete clearance rate of AK lesions at the Day 57 visit. A patient with no clinically visible AK lesions in the selected treatment area was defined to have complete clearance.

**Secondary Endpoint:**
Partial clearance rate of AK lesions at the Day 57 visit. A patient with a 75% or greater reduction in the number of clinically visible AK lesions identified at baseline, in the selected treatment area was defined to have partial clearance.

**Additional Endpoint:**
The percent change from baseline to Day 57 in the total number of AK lesions.

**Exploratory:**
Patient-reported outcomes, including the Treatment Satisfaction Questionnaire for Medication (TSQM) at Day 57 and the Skindex-16 Dermatological Survey at baseline and Days 8, 29, and 57.

**Safety:**
- Incidence rate of AEs, serious adverse events (SAEs) and AEs leading to discontinuation of study medication as recorded throughout the study;
- Incidence rate and grade of LSRs, pigmentation and scarring following study treatment;
- Results of clinical laboratory tests, vital signs, physical examinations, and electrocardiogram (ECG) findings.

**Statistical Methods:**
The primary efficacy analysis was based on the intent-to-treat (ITT) population. In the ITT population, patients were counted in the treatment group to which they were randomized, regardless of receiving any dose of study medication.

For the analyses of complete and partial clearance, all missing values were imputed using last observation carried forward (LOCF). Baseline data were carried forward if no postbaseline data existed for the patient. That is, those patients were considered to have not achieved complete or partial clearance.

The safety analysis was based on the safety population, which was defined as 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.

All treatment comparisons were tested with two-tailed tests and a 0.05 significance level.
Efficacy:
The primary efficacy endpoint was complete clearance rate at Day 57 of all clinically visible AK lesions in the
selected treatment area. The complete clearance rate was compared between treatment groups using the Cochran-
Mantel-Haenszel (CMH) test, stratified by analysis site. The secondary efficacy endpoint was the partial clearance
rate of AK lesions at Day 57. The statistical analysis was the same as that used for the primary efficacy endpoint.
An additional efficacy endpoint was the percent change from baseline to Day 57 in the total number of AK lesions.
The percent change from baseline in the number of AK lesions was summarized for each treatment group.
Summaries were also provided by each anatomical location.

Patient-Reported Outcomes:
The TSQM transformed scores at Day 57 and the Skindex-16 Dermatological Survey transformed scores at baseline
and Days 8, 29, and 57 were summarized by treatment group. The transformed scores were treated as a continuous
variable and analyzed using analysis of variance (ANOVA) with treatment, anatomical location, and analysis site as
factors to test for treatment effect.

Safety:
The safety endpoints included: incidence rate of patients who experienced AEs, SAEs and AEs leading to
discontinuation of study medication; incidence and grade of LSRs and/or pigmentation/scarring; changes in clinical
laboratory tests, vital signs, physical examinations, and ECG findings. The treatment effect was explored by
inspection of observed means or rates for the treatment groups.

Summary of Results:
Efficacy:
The primary efficacy endpoint was complete AK lesion clearance overall (face and scalp combined) at Day 57. The
PEP005 Gel group demonstrated a statistically significant, higher complete clearance rate versus vehicle gel
(47% compared to 5%, p < 0.001, CMH test stratified by analysis site) based on the ITT population. The results for
the PP population were consistent with the results for the ITT population. Patients treated on the face with PEP005
Gel demonstrated a statistically significant, higher complete clearance rate compared to vehicle gel-treated patients
(52% versus 5%, p < 0.001, Fisher's Exact test). For scalp-treated patients, the difference between the treatment
groups was also statistically significant (29% versus 4%, p = 0.031, Fisher's Exact test).
The secondary efficacy endpoint was partial (≥75% reduction) AK lesion clearance at Day 57. Consistent with the
primary endpoint, the PEP005 Gel group demonstrated a statistically significant, higher partial clearance rate versus
vehicle gel (68% compared to 8%, p < 0.001, CMH test stratified by analysis site) based on the ITT population. The
results for the PP population were consistent with the results for the ITT population. Patients treated on the face
with PEP005 Gel demonstrated statistically significant, higher partial clearance rates than vehicle gel patients
(74% versus 9%, p < 0.001, Fisher's Exact test). For scalp-treated patients, the difference between the treatment
groups was also statistically significant (45% versus 4%, p < 0.001, Fisher's Exact test).
The median percent reduction in the number of AK lesions compared to baseline overall (face and scalp combined)
was substantially greater for the PEP005 Gel group (87%) versus 0% in the vehicle group. For patients treated on
the face, the median reduction was 100% for the PEP005 Gel group versus 0% in the vehicle group. For patients
treated on the scalp, the median reduction was 63% for the PEP005 Gel group versus 0% in the vehicle group.
In the subgroup analyses, the complete clearance rate for each treatment group was analyzed by geographic region
(US or AUS), gender, age group (<65 or ≥65 years), baseline AK lesion count (4, 5, 6 or 7, 8), skin type
(Fitzpatrick I/II or III/IV/V/VI), and analysis site. Findings showed a higher complete clearance rate for PEP005
Gel-treated patients compared to vehicle patients in each category; the only category that did not show statistical
significance was the geographic region of Australia.
Patient reported outcomes included the TSQM and the Skindex-16 Dermatology Survey. Statistically significant,
higher mean patient global satisfaction scores, measured by the TSQM, were seen in the PEP005 Gel group
compared to the vehicle gel group (p < 0.001). For the Skindex-16 Dermatology Survey, a statistically significant
difference was seen with PEP005 Gel-treated patients less bothered by each of the three domains (symptoms, emotions, and functioning) compared to vehicle gel; the positive effect was seen at Day 29 (p < 0.001, each domain) and continued at Day 57 (p < 0.001, each domain).

Safety:
PEP005 Gel, 0.015% was, in general, well tolerated when applied once daily for three consecutive days.

Compliance to the treatment regimen was 99% for the PEP005 Gel group and 100% for the vehicle gel group. No deaths occurred during the study. One patient in the PEP005 Gel group experienced two serious adverse events (hip arthroplasty and myocardial infarction); both were considered by the investigator to be not related to study medication. Two patients who received PEP005 Gel discontinued study medication due to application site reactions. One patient experienced pain and stinging which started on Day 1, and was considered by the investigator to be severe and definitely related to study medication. The patient applied study medication for two days. The adverse event resolved without sequelae on Day 7. The other patient experienced burning and pruritus which started on Days 1 and 2, respectively. Both events were considered by the investigator to be moderate and definitely related to study medication. The patient only applied study medication for one day. The burning resolved without sequelae on Day 3 and the pruritus resolved without sequelae on Day 7.

Application site reactions were the most common treatment-related AEs reported for the PEP005 Gel patients, with pain and pruritus reported as the most frequent application site events. Application site infection occurred in two PEP005 Gel patients, each case was first documented at Day 4, considered mild in severity, and resolved within 4 days. Paresthesia at the application site occurred in two patients and discomfort, discharge, and swelling at the application site occurred in only one patient each. Other treatment-related events included eyelid oedema, eye oedema, and periorbital edema. The majority of treatment-related adverse events were mild or moderate in severity. Only one PEP005 Gel-treated patient (1%) experienced two treatment-related events that were considered severe (pain and stinging at the application site which led to discontinuation of study drug). All treatment-related events resolved without sequelae.

The most common LSRs were erythema (99% for PEP005, 72% for vehicle), flaking/scaling (97% for PEP005, 62% for vehicle) and crusting (82% for PEP005, 10% for vehicle). Grade 4 LSRs were observed in 25% of the PEP005 Gel group. Mean composite LSR scores (maximum score of 24) peaked at Day 4 with a score of 8.08 for the PEP005 Gel group and 1.17 for the vehicle gel group; by Day 29, scores were lower than baseline levels. All LSRs resolved without sequelae.

Hypopigmentation and hyperpigmentation assessments remained unchanged from baseline at Day 57 in the majority of patients. Five patients (one PEP005 patient and four vehicle patients) had hypopigmentation or hyperpigmentation at Day 57 which was not present at baseline. No treatment emergent scarring was observed. One patient in the vehicle group had abnormal proliferation in the treatment area which was noted on Day 57. The lesion was excised on Day 99 and confirmed to be basisquamous carcinoma which was recorded as an adverse event. No further followup was necessary.

No clinically meaningful differences were observed between the treatment groups when actual and change from baseline values were assessed for hematology and serum chemistry tests, vital signs, and interval-valued ECG parameters. Results of physical examinations showed no clinically relevant findings.

Conclusion:
The following conclusions are based on the results of this study:

- The treatment regimen of PEP005 Gel, 0.015% applied daily for three consecutive days was shown to be effective in completely clearing a contiguous 25cm² treatment area of AK lesions on the head (face and scalp).
- Other efficacy endpoints provided confirmation of the treatment effect. The partial clearance rate was significantly higher in patients treated with PEP005 Gel and the median percent reduction from baseline in the number of AK lesions was substantially greater.
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- Patient compliance with the treatment regimen was high; 99% of PEP005 Gel patients completed the full course of therapy.
- PEP005 Gel, 0.015%, in general, appeared to be safe and well-tolerated when used to treat AK lesions on the face and scalp. No serious adverse events were considered treatment-related. All treatment-related application site adverse events and local skin responses resolved without sequelae.

**Final Report Date:** 8 September 2010